Brucella endocarditis – a registry study

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Abstract

Background: A zoonotic infection caused by Brucella spp., brucellosis, is endemic in some areas of the world, like in our country. One of the most devastating conditions related to this infection is endocarditis, although it is rare. Unfortunately, adequate studies on the characteristics of Brucella endocarditis have not been performed. In addition, there was no consensus on optimal type and duration of medical and interventional therapies.

Aim: To answer the following questions: what are the clinical characteristics of Brucella endocarditis, which type of therapy should be performed, and can an alternative antibiotic regimen be applied?

Methods: Patients with the diagnosis of Brucella endocarditis were included in the study during a 6-year period. A total of 10 patients were interrogated for their signs, symptoms, drug use, and clinical conditions. In addition, baseline clinical and laboratory characteristics of the patients were evaluated.

Results: All patients in the study were male with a mean age of 55.9 ± 12.7 years. Hospitalisation and total follow-up periods were 52.6 ± 11.2 and 80.6 ± 29.0 days, respectively. The most frequently presenting symptom was fever (60%). Dyspnoea and fatigue were the other frequent symptoms in descending order. Valve pathology was present in 70% of the study population. The aortic valve was affected more than the mitral valve. Affected mitral valves had rheumatic disease whereas only 57% of the aortic valves had underlying pathology. Isolation of Brucella spp. was possible in 20% of the patients. Mortality rate was 30% in our study; 20% of the patients were on medical follow-up without disease progression and with clinical stability, 60% of patients were on a combination therapy with a tetracycline group, a rifampicin, and a third-generation cephalosporin. Patients who took this combination and underwent aortic valve replacement had good clinical results with a mortality rate of 20%. The 30% of patients were on a combination therapy with a tetracycline group, rifampicin, and an aminoglycoside group. Mortality rate with this combination was 33%, although the success rate was 67%.

Conclusion: Brucella endocarditis should be considered in the differential diagnosis in patients with vegetations on the cardiac valves, especially in endemic areas. Optimal therapy seems to be a combination of antibiotics and surgery, although medical therapy can be an alternative, especially in stable patients. Addition of a third-generation cephalosporin instead of aminoglycoside to the combination therapy is an alternative.

Key words: Brucella, characteristics, endocarditis, therapy

Introduction

A zoonosis, Brucella, causes a special form of infectious disease named brucellosis. Any organ system may be affected, although the musculoskeletal, especially osteoarticular part, is the most commonly affected. Involvement of the cardiovascular system is relatively rare. Endocarditis associated with this zoonotic infection is the most commonly seen pathology of the cardiovascular system [1].

As seen in other pathogens causing infective endocarditis, the mortality rate of Brucella-related endocarditis is high even if modern therapeutic methods such as the latest generation antibiotics and surgical techniques are used. Because of limited data associated with Brucella endocarditis, there is no formed consensus about type and duration of optimal antimicrobial and interventional therapies [2].

We present here a registry study in which a relatively large series of patients with Brucella endocarditis is described, and the most suitable choice of treatment modality is discussed. We performed the registry study to answer: what are the clinical characteristics of Brucella endocarditis, which type of therapy should be performed, and can an alternative antibiotic regimen be applied?
Methods

Study population

Between 2002 and 2007, 112 cases with infective endocarditis admitted to our department were investigated, and patients with the diagnosis of Brucella endocarditis were included in the study. A total of 10 patients (8.9% of cases with endocarditis) with the diagnosis of Brucella endocarditis were studied. Exclusion criteria included the diagnosis of endocarditis caused by any other pathogen. All patients were interrogated for their signs and symptoms. Vital signs and NYHA functional class of patients were recorded. All patients were also interrogated for any drug use. In addition, ECG records were obtained.

Diagnosis of Brucella endocarditis

Diagnosis of endocarditis has been made according to the Duke’s criteria [3]. Modified Duke's criteria were used after June 2005 [4]. Specifically, isolation of Brucella spp. in blood culture and pathological specimens, determination of specific antibodies with Wright’s seroagglutination ≥ 1/160, and echocardiographic appearance concordant with endocarditis were used for the diagnosis. A Wright agglutination test in a titre of 1/160 or higher is very sensitive and specific for the diagnosis of brucellosis [5]. All obtained specimens were incubated for as long as 21 days. Blood samples were cultured in an automatic system. Subcultures were performed on Brucella agar. Suspect colonies were identified by their morphology, Gram stain, oxidase, catalase and urease tests, and positive agglutination with specific antiserum.

Laboratory examination

Fasting peripheral venous blood samples were obtained at admission from all patients for the measurement of haemoglobin, haematocrit, white blood cell, erythrocyte sedimentation rate, fibrinogen, fasting plasma glucose, urea, creatinine, uric acid, aspartate amino transferase, alanine amino transferase, lactate dehydrogenase, total protein, and albumin values.

Echocardiographic evaluation

All patients underwent transthoracic and transoesophageal echocardiographic examination. Gross pathologies associated with endocarditis were recorded. Other routinely performed echocardiographic parameters such as left ventricular ejection fraction, and internal diameters of the chambers were also recorded.

Antimicrobial therapy

Other than the department of cardiology (departments of cardiovascular surgery, infectious diseases, and microbiology), also participated in the therapeutic decision process. At least 4 weeks of combination antibiotic therapy before the operation was decided. After surgery, if the infectious condition continued in removed pathological material, histopathological antimicrobial therapy was continued at least 6 weeks postoperatively. If no evidence of infection was found, the therapy was stopped after an additional 2 weeks postoperatively.

Statistical analysis

Data were analysed with the SPSS software version 15.0 for Windows (SPSS Inc., Chicago, Illinois). Continuous variables are presented as mean ± SD and categorical variables as frequency and percentage. The χ² test was used to compare categorical variables. A two-tailed p-value of < 0.05 was considered as statistically significant.

Results

Baseline characteristics

All patients in the study were male, with a mean age of 55.9 ± 12.7 years (range 32-66 years). The minimum hospitalisation period was 10 days, and the minimum follow-up period was 48 days. According to mean haemoglobin level, the study population had anaemia without leukocytosis. Mean erythrocyte sedimentation rate was within normal limits. Mean left ventricular ejection fraction was slightly impaired. All but one patient had sinus rhythm. The most frequent symptom was fever (60%) followed by dyspnoea and fatigue (Table I).

Patient no. 1

This 32-year-old patient was referred to our department with severe decompensated heart failure symptoms (NYHA class IV) refractory to medical therapy. The initial primary health centre started a penicillin group antibiotic agent because of fever of undetermined origin. Transthoracic and transoesophageal echocardiography showed a vegetation on the aortic valve with a size of 0.9 × 0.7 cm. In addition, 3+ aortic regurgitation was present. Blood cultures were negative. However, Wright’s agglutination test was positive. Combination therapy with a tetracycline group, rifampicin, and a third-generation cephalosporin was started by the department of infectious diseases. Surgical intervention was planned but patient’s clinical condition deteriorated. The patient died at the 4th week of therapy because of rapid progression of heart failure.

Patient no. 2

A 35-year-old patient had subfebrile and sometimes high (> 38°C) body temperature lasting approximately 4 months. He was admitted to our department with dyspnoea, palpitations, and the previous diagnosis of bicuspid aortic valve. No previous use of an antibiotic agent was determined. Transthoracic and transoesophageal echocardiography showed a vegetation on the bicuspid aortic valve with a size of 0.4 × 0.5 cm. In addition,
2-3+ aortic regurgitation was present. Blood cultures were negative, Wright’s agglutination test was positive. Combination therapy with a tetracycline group, rifampicin, and a third-generation cephalosporin was started in the department of infectious diseases. However, the patient died at the 2nd week of therapy because of rapid progression of the aortic regurgitation and heart failure. Aortic valve replacement surgery was also planned for the patient. However, the patient died during preparation for the surgery.

Patient no. 3

This 61-year-old patient was followed for rheumatic mitral valve disease. During a routine clinical visit, transthoracic echocardiography showed a vegetation-like mass on the mitral valve. In addition, transoesophageal echocardiography revealed a vegetation, 1.1 × 0.7 cm in size. In addition, 2+ mitral regurgitation was present. From his medical history we learned that he had arthritic pain and fatigue. No previous use of an antibiotic agent was determined. Blood cultures were negative, Wright’s agglutination test was highly titrated positive. Combination therapy with a tetracycline group, rifampicin, and an aminoglycoside group antibiotic was started in the department of infectious diseases. The patient underwent valve replacement surgery with a mechanical valve at the 5th week of therapy.

Patient no. 4

A 66-year-old patient with a bioprosthesis in the aortic position was admitted to our department with fever, dyspnoea, and fatigue that had continued for a week. He started to take a macrolide group antibiotic for a possible upper respiratory tract infection by himself. Transthoracic and transoesophageal echocardiography showed a vegetation on the aortic bioprosthetic valve with a size of 0.5 × 0.5 cm. In addition, 2+ aortic regurgitation was present. Blood cultures were negative; Wright’s agglutination test was highly titrated positive. Combination therapy with a tetracycline group, rifampicin, and a third-generation cephalosporin was started in the department of infectious diseases. The bioprosthesis was changed for a mechanical valve at the 6th week of antimicrobial therapy.

Patient no. 5

A 62-year-old male was referred to our department with a probable diagnosis of infective endocarditis. A cardiac murmur and a history of fever were found, and penicillin and gentamicin antibiotics were started in another hospital. Transthoracic and transoesophageal echocardiography showed a vegetation on the native aortic valve with a size of 0.5 × 0.5 cm. In addition, 3+ aortic regurgitation was present. Brucella abortus was
isolated from the blood cultures. Wright’s agglutination test was also highly titrated positive. Combination therapy with a tetracycline group, rifampicin, and a third-generation cephalosporin was started by the department of infectious diseases. At the 6th week of antibiotic therapy, the patient underwent aortic valve replacement with a mechanical valve.

**Patient no. 6**

A 61-year-old male patient with a degenerative aortic valve and 3-4+ aortic regurgitation was admitted to our department with subtle complaints of fatigue and weight loss. No previous use of an antibiotic agent was determined. Transthoracic and transoesophageal echocardiography showed a vegetation on the degenerative, non-coaptated aortic valve with a size of 0.8 × 0.8 cm. Blood cultures were negative; however, Wright’s agglutination test was highly titrated positive. Combination therapy with a tetracycline group, rifampicin, and a third-generation cephalosporin was started in the department of infectious diseases. At the 7th week of antibiotic therapy, the patient underwent aortic valve replacement with a mechanical valve.

**Patient no. 7**

This 65-year-old male with a history of rheumatic mitral disease and previous closed mitral commissurotomy was referred to our department with a diagnosis of culture-negative infective endocarditis. A combination therapy with penicillin and gentamicin was started, and for a possible intervention, the patient was referred to us. Transthoracic and transoesophageal echocardiography showed a vegetation on the rheumatic mitral valve with a size of 1.0 × 0.7 cm. In addition, 2-3+ mitral regurgitation was present. Blood cultures were negative; however, Wright’s agglutination test was highly titrated positive. Combination therapy with a tetracycline group, rifampicin, and an aminoglycoside group antibiotic was started by the department of infectious diseases. At the 6th week of antibiotic therapy, the patient underwent aortic valve replacement with a mechanical valve.

**Patient no. 8**

A 61-year-old male patient was admitted to our emergency department with high fever and deterioration of his general condition. He had a degenerative aortic valve with mild to moderate stenosis. No information could be taken about previous antimicrobial use. Transthoracic and transoesophageal echocardiography showed a vegetation on the degenerative stenotic aortic valve with a size of 0.6 × 0.4 cm. Blood cultures were negative, Wright’s agglutination test was positive. Combination therapy with a tetracycline group, rifampicin, and a third-generation cephalosporin was started in the department of infectious diseases. At the 5th week of antibiotic therapy, the patient underwent aortic valve replacement with a mechanical valve.

**Patient no. 9**

This patient was also admitted to our department with high fever, dyspnoea, and deterioration of general condition. No antibiotic use for the last 3 months was present. Transthoracic and transoesophageal echocardiography showed a rheumatic mitral valve and a vegetation on the ventricular surface of this deformed valve with a size of 1.4 × 1.2 cm. In addition, 3+ mitral regurgitation was present. Blood cultures were negative; however, Wright’s agglutination test was highly titrated positive. Combination therapy with a tetracycline group, rifampicin, and an aminoglycoside group antibiotic was started in the department of infectious diseases. Initially, medical follow-up was planned because of clinical improvement. However, clinical deterioration started by the end of the 2nd week. Emergent surgery was decided but at the 3rd week of antibiotic therapy, the patient died from ventricular arrhythmia.

**Patient no. 10**

A 50-year-old patient was referred to our department for further evaluation of a mass-like lesion on the aortic valve. He was asymptomatic other than indistinctly fatigued. He had no history of any antibiotic use. Transthoracic and transoesophageal echocardiography showed a native aortic valve and a vegetation on the valve with a size of 0.9 × 0.9 cm. In addition, 1-2+ aortic regurgitation was present. Blood cultures were negative, Wright’s agglutination test was positive. Combination therapy with a tetracycline group, rifampicin, and an aminoglycoside group antibiotic was started in the department of infectious diseases. Because of good general condition and no progression of the vegetation, we decided to complete the given antibiotic regimen to 8 weeks with medical follow-up (Table II).

**Analysis of the disease and end-points**

**Valves**

The 70% of patients had underlying valve pathology for endocarditis in our study. *Brucella* endocarditis affected the aortic valves more than the mitral valves in our study, as expected (70%). The 43% of the infected aortic valves had no predisposing pathology. All the affected mitral valves had rheumatic pathology. One patient had a bicuspid aortic valve. In addition, only one patient had a prosthetic valve, a bioprosthesis, as a predisposing factor. Lastly, two patients had degenerative aortic valves.

**Microbiology**

*Brucella* spp. could be isolated only in 2 (20%) patients. In addition, these 2 patients had been on previous
antimicrobial therapy. No previous use of an antibiotic has been determined in 6 of 10 patients.

Valve replacement and mortality

Mortality rate was 30% in our study population. Two patients have been followed up medically without clinical deterioration (20%). All patients who underwent valve replacement surgery received a mechanical valve.

Antibiotics

The 60% of patients received a combination therapy with a tetracycline group [one with doxycycline (200 mg/day), the dose of tetracycline was 4 × 0.5 g], rifampicin (900 mg/day), and a third-generation cephalosporin (ceftriaxone 1 g/day). Patients taking this combination who underwent aortic valve replacement had good clinical results. Mortality rate with this combination was 33%. Three patients had the combination with a tetracycline group (4 × 0.5 g), rifampicin (900 mg/day), and an aminoglycoside group (streptomycin, 1 g/day for 21 days) antibiotic. Of these, 1 died, 1 had mitral valve replacement, and 1 had medical follow-up without clinical deterioration. Success rate of this combination was 20%, and mortality rate – 33%. Only 1 patient followed up medically had a combination with a tetracycline (4 × 0.5 g) group and rifampicin (900 mg/day) (10%) (Figure 1).

Lastly, there was evidence of anti-Brucella antibodies in all cases. The diagnosis was confirmed microbiologically and/or histologically in those patients who underwent cardiac surgery. No relapse has been seen in successfully treated patients.

Discussion

Brucellosis is endemic in our country. Various studies and case reports have been reported related to this infestation from Turkey [5, 6]. In fact, there may be many more cases with undiagnosed brucellosis and related endocarditis in rural areas.

Brucella endocarditis is a rare type of endocarditis. In endemic regions, its prevalence is higher than in non-endemic parts of the world. It has a much higher mortality rate than endocarditis caused by other pathogens due to its rapid and wide tissue destruction. In addition, the high mortality rate might be due to late diagnosis of the infection, because various diseases such as some malignancies might be considered as the cause instead of brucellosis.

Data about this unusual type of infection are limited. Case reports have been generally presented for this clinical entity. Case series have also been presented with relatively small numbers of patients. Because of the nature of the disease, no randomised study can be performed.

As is usual in brucellosis, young men were infected more frequently than females [7, 8]. All the patients in our study were male, as expected. In addition, they all had
Brucella endocarditis is a rare but serious complication of brucellosis. The diagnosis of Brucella endocarditis can be challenging, as the organism has a slow growth rate, and it also needs specific environment for growth. Blood culture should be obtained even if previous antimicrobial use is present. Patients having positive blood cultures in our study had a history of ingestion of contaminated milk or milk products, more commonly non-pasteurised cheese.

Haematological and biochemical indices were similar to previous studies [1].

The predominant symptom has been fever in previous studies, with a rate of 100% [7, 8]. However, the prevalence of fever in our study was 60%. There might be some reasons for this: firstly, patients' cooperation about their symptoms might not be sufficient, and previous use of antibiotic agents might mask the symptoms.

The predominantly involved valve in Brucella endocarditis is the aortic one, as in our study [7]. All patients with mitral involvement had rheumatic pathology as seen in the study by Reguera et al. [7]. In the study of Reguera et al., 33% of the patients with aortic endocarditis had underlying valve pathology. One patient had bicuspid valve, the remaining 2 had rheumatic valves [7]. However, in our study, 57% of the patients with aortic involvement had underlying pathology. If we did not have assumed the degenerative valves as an underlying pathology, the percentage would have decreased to 29.

The diagnosis of culture-negative endocarditis can be easily made in the case of brucellosis, because the organism has a slow growth rate, and it also needs a special environment for growth. Blood culture should be obtained even if previous antimicrobial use is present. Patients having positive blood cultures in our study had an antibiotic previously. In addition, no previous use of an antibiotic agent was not an advantage to isolate the organism in our study. Clinical signs and symptoms with a positive serology were the points for the diagnosis of the disease in a patient with demonstrable vegetations in our study. Therefore, serologic examination becomes more important in the diagnosis of Brucella endocarditis. A Wright agglutination test in a titre of 1/160 or higher is very sensitive and specific, as much as 100%, for the A Wright agglutination test in a titre of 1/160 or higher is important in the diagnosis of Brucella endocarditis. Therefore, serologic examination becomes more important in the diagnosis of Brucella endocarditis. A Wright agglutination test in a titre of 1/160 or higher is very sensitive and specific, as much as 100%, for the diagnosis of brucellosis [5].

Brucella endocarditis produces highly destructive lesions of the valve structure; this might explain the high fatality rate for Brucella endocarditis. The total mortality rate was 30% in our study despite optimal medical therapy.

In the treatment of brucellosis, current knowledge recommends a combination of a tetracycline group, rifampicin, and an aminoglycoside group [9]. In our study, we demonstrated that addition of a third-generation cephalosporin, ceftriaxone, to the combination of a tetracycline group and rifampicin was also effective. Because of renal toxicity of aminoglycosides, ceftriaxone can be a good alternative. Third-generation cephalosporin (ceftriaxone 1 g/day) was used in our study. Because of its very good pharmacokinetic profile, this antimicrobial agent might be used especially in patients with impaired renal function. In patients allergic to penicillin, the use of cephalosporin can be dangerous.

In the treatment of Brucella endocarditis, the combination of antimicrobial therapy and surgery has been generally recommended, although some cases with successful medical treatment have been reported, as in our study [7, 8].

Study limitations

The major limitation of the study was that it was a registry study, and a relatively small number of the studied patients.

Conclusion

Brucella endocarditis remains an unusual but serious complication of brucellosis. Brucella endocarditis should be considered in the differential diagnosis if patients have a vegetation on the cardiac valves, especially in endemic areas. Optimal therapy seems to be a combination of antibiotics and surgery, although medical therapy can be an alternative, especially in stable patients. Also, addition of a third-generation cephalosporin instead of aminoglycoside to the combination therapy is an alternative.

References

Infekcyjne zapalenie wsierdzia spowodowane brucelozą – rejestr

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Streszczenie

Wstęp: Brucelosa występuje w różnych endemicznych rejonach świata, w tym w Turcji. Jednym z najcięższych, ale sporadycznie spotykanych powikłań bruceloz jest infekcyjne zapalenie wsierdzia (IZW). W piśmiennictwie nie ma badań opisujących w pełni to powikłanie brucelozy.

Cel: Przedstawienie klinicznego obrazu IZW wywołanego brucelozą, ocena skuteczności leczenia, w tym możliwości zastosowania niestandardowej antybiotykoterapii.

Metody: W ciągu 6 lat chorzy z IZW wywołanym brucelozą włączani byli do specjalnego rejestru. W sumie grupa badana składała się z 10 chorych, u których poddano analizie wszystkie dostępne dane kliniczne i laboratoryjne.

Wyniki: Wszyscy chorzy byli płci męskiej, a ich średni wiek wynosił 55,9 ± 12,7 roku. Czas hospitalizacji i obserwacji ambulatoryjnej wynosił odpowiednio 52,6 ± 11,2 i 80,6 ± 29,0 dni. Najczęściej spotykanym objawem przy przyjęciu była gorączka – 60% chorych, a następnie duszność i męczliwość. Wady zastawkowe wykryto u 70% chorych. Zastawka aortalna zajęta była procesem chorobowym częściej niż zastawka mitralna. Proces reumatyczny dotyczył wszystkich zajętych zastaweń mitralnych i 57% zastawek aortalnych. Izolacja drobnoustroju Brucella spp. możliwa była u 20% chorych. Śmiertelność wyniosła 30%. U 20% chorych stosowano leczenie farmakologiczne, uzyskując stabilizację choroby. U 60% chorych stosowano złożoną antybiotykoterapię, w skład której wchodziły tetracykliny, ryfampicyna i cefalosporyna trzeciej generacji. Chorzy leczeni takim zestawem antybiotyków, u których następnie wymieniono zastawkę aortalną, rokowali względnie dobrze, a śmiertelność wyniosła 20%. U 30% chorych stosowano tertracykliny, ryfampicynę i aminoglikozyd – w tej grupie śmiertelność wyniosła 33%.

Wnioski: Infekcyjne zapalenie wsierdzia spowodowane brucelozą powinno być zawsze brane pod uwagę, jeśli stwierdza się wegetacje na zastawkach serca, szczególnie u osób pochodzących z rejonów endemicznych. Optymalnym postępowaniem wydaje się połączenie antybiotykoterapii i wymiany zastawki, aczkolwiek samo leczenie farmakologiczne może być skuteczne, szczególnie u chorych w stanie stabilnym. Ponadto wydaje się, że korzystne może być zastosowanie cefalosporyn trzeciej generacji zamiast aminoglikozydów.

Słowa kluczowe: infekcyjne zapalenie wsierdzia, brucelosa

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