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Original Article

Internal Medicine Section

Clinical Manifestations and Treatment Outcomes of Brucella Endocarditis: A Retrospective Cohort Study at a Tertiary Cardiac Centre in Bengaluru, Karnataka, India

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ABSTRACT

Introduction: Brucella is a rare cause of Infective Endocarditis (IE), requiring prompt early recognition and treatment to prevent life-threatening complications. Diagnosis is often missed or delayed, leading to an increase in cardiac morbidity and mortality.

Aim: To analyse the clinical profile, laboratory parameters, cardiac manifestations, management patterns, and outcomes of Brucella endocarditis.

Materials and Methods: A retrospective cohort study was conducted at the Department of Cardiology, Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bangaluru, Karnataka, India on patients with blood culture-confirmed Brucella endocarditis, diagnosed using modified Duke's criteria between January 2010 and December 2021. The present study evaluated the clinical presentation, treatment modalities, and outcomes. Descriptive statistical analyses were performed.

Results: A total of 34 cases were identified during the study period. The mean age of the patients was 35.6±14 years (age range: 15-66 years), with 82.4% males and 17.6% females. Underlying valvular heart disease was present in 82.4% of the patients, while 17.6% had no pre-existing valvular heart disease. Both aortic and mitral valves were involved with equal frequency. All patients presented with fever. Most patients had a normal leukocyte count (61.8%). Thrombocytopenia (32.3%) and pancytopenia (17.6%) were also observed. Large vegetations (>1 cm) were seen in 38.2% of patients, and complications related to IE were observed in 35.2%. The majority of patients (82.4%) were managed medically alone in the acute phase. The antibiotic regimen of doxycycline with rifampicin combined with intravenous gentamicin was used in the majority of the patients. The observed mortality rate was 17.6%.

Conclusion: Brucella endocarditis can present with thrombocytopenia/pancytopenia along with normal or reduced leukocyte count. The addition of intravenous gentamicin to oral therapy may reduce relapse rates.

Keywords: Brucellosis, Doxycycline, Vegetations

INTRODUCTION

Human brucellosis is a zoonotic disease transmitted through the consumption of infected unpasteurised milk, dairy products, inhaled aerosols, and direct contact with infected animal parts [1]. The causative pathogen is a gram-negative intracellular bacillus of the genus Brucella, which leads to chronic granulomatous infection with multiorgan involvement [1]. The bacteria usually grow in the regional lymph nodes and enter the bloodstream through the ductus thoracicus [1]. Brucellosis cases have been reported from countries across the globe, with the highest concentration of cases in Central Asia and the Mediterranean region [1-3].

Cardiovascular manifestations of brucellosis include Infective Endocarditis (IE), myocarditis, and pericarditis, occurring in about 2% of infections [4]. IE is the major cause of mortality in brucellosis, accounting for 70-80% of deaths [5]. Being a slow-growing, fastidious organism, and given the limitations of serological tests, the diagnosis of brucellosis poses significant challenges and is often missed [1]. The prevalence of Brucella endocarditis is 1.3-1.7% [3]. Data from India is limited to case reports and case series [3,6,7]. Haematological parameters and treatment outcomes have not been evaluated in India. The present study aimed to evaluate the clinical manifestations, cardiac involvement, treatment modalities, and outcomes in Brucella endocarditis from a tertiary cardiac care centre in India.

MATERIALS AND METHODS

A retrospective cohort study was conducted at the Department of Cardiology, Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bangaluru, Karnataka, India by reviewing medical records. Patients diagnosed with Infective Endocarditis (IE) and isolation of Brucella species in blood culture between January 2010 and December 2021 at Sri Jayadeva Institute of Cardiovascular Sciences and Research, India, were included in the study. The study was planned in the year 2022, with data analysis and interpretation completed in the same year. A total of 34 patients were included in the study. Institutional Ethics Committee approval (SJICR/EC/2021-2022/034) was obtained for the study.

Inclusion criteria:

- Patients diagnosed with definite IE as per the modified Duke criteria [8,9].
- Isolation of Brucella species in blood culture.

Exclusion criteria: Patients with only serological diagnosis (i.e., elevated antibody titers) of brucellosis but without organism isolation in blood culture were excluded.

Study Procedure

Blood culture isolation and identification of Brucella species were performed using the automated Bact/Alert culture media and

VITEK 2 system (Biomerieux, USA) [10,11]. The Standard Agglutination Test (SAT) [10,11], which measures total agglutinating antibodies {Immunoglobulin M (IgM) and Immunoglobulin G (IgG)}, was used to detect antibody titers. A single titer of >1:640 was considered significant [11,12].

Clinical symptoms and signs at presentation were evaluated. Dyspnoea was graded based on the New York Heart Association (NYHA) class [13]. Anaemia was defined as a haemoglobin value of <12 g/dL in females and <13 g/dL in males. Thrombocytopenia was defined as a platelet count of <1.5 lac/mm^3. Liver transaminase elevation of >2 times the upper limit of normal was considered significant. Serum creatinine >1.5 mg/dL was considered as renal impairment. Treatment regimens and antibiotics used, along with dosages, were evaluated. Relapse and mortality rates were studied. Medical management included treatment with antibiotics and heart failure medications.

STATISTICAL ANALYSIS

Descriptive statistical analyses were conducted for variables of interest. Results of continuous measurements are presented as mean or median. Results of categorical measurements are presented as numbers (%). For data analysis, Statistical Package for Social Sciences (SPSS) 18.0 statistical software and the R environment version 3.2.2 were used.

RESULTS

Between January 2010 and December 2021, a total of 34 patients with definite Infective Endocarditis (IE) and Brucella isolate in blood culture were identified and included in the study. The mean age of the population was 35.6±14 years (age range 15-66 years), with 82.4% males and 17.6% females. The symptoms at presentation and underlying heart disease are summarised in [Table/Fig-1]. A history of fever was present in all patients at presentation. The median duration of fever was one month, and the longest duration of fever was seven months.

Parameters	Values
Age (in years)	**35.6±14**
Gender distribution (%)	
Male	82.4
Female	17.6
Fever, n (%)	34 (100) Median duration: 1 month
Dyspnoea, NYHA, n (%)	
Class II	17 (50.0)
III	8 (23.5)
IV	9 (26.5)
Arthralgia n (%)	6 (17.6)
Underlying structural heart disease n (%)	
None	6 (17.6)
RHD	22 (64.7)
Prosthetic valve	5 (14.8)
CHD	1 (2.9)

[Table/Fig-1]: Baseline characteristics and symptoms.
NYHA: New York heart association; RHD: Rheumatic heart disease; CHD: Congenital heart disease

The majority of patients (82.4%) had underlying structural heart disease, with rheumatic heart disease being the most common (64.7%). The blood investigations and laboratory parameters are summarised in [Table/Fig-2]. Normal leukocyte count was seen in most patients (61.8%), and thrombocytopenia was noted in about one-third of the patients. About one-third of the patients had renal impairment at presentation, defined as a serum creatinine value of more than 1.5 mg/dL. Both aortic and mitral valves were involved with equal frequency (41.2%), as shown in [Table/Fig-3]. Tricuspid and pulmonary valve involvement were not observed. Large vegetations (size >1 cm) were seen in 38.2% of patients, and complications related to IE were noted in 35.2% of the patients [Table/Fig-3]. Antibody titers measured by the Standard Agglutination Test (SAT) were >1:640 in all patients. Most patients (82.4%) were managed medically in the acute phase, and the antibiotic protocols are shown in [Table/Fig-4]. The overall mortality rate noted in the present study was 17.6%, with relapse of the disease seen in 5.8% of the patients. All patients had heart failure with severe valve regurgitation.

Investigation	n (%)
Leucocyte count	
Normal	21 (61.8)
Leucocytosis	8 (23.5)
Leucopenia	5 (14.7)
Thrombocytopenia	11 (32.3)
Anaemia	19 (55.8)
Pancytopenia	6 (17.6)
Renal impairment	11 (32.3)
Transaminase elevation	6 (17.6)
Splenomegaly	8 (23.5)
Duration of blood culture growth	Mean: 5.8 days

[Table/Fig-2]: Blood investigations and laboratory parameters.

Valve involvement and complications	n (%)
Valve involved	
Aortic	14 (41.2)
Mitral	14 (41.2)
Both	2 (5.8)
Prosthetic	4 (11.8)
Vegetation size	
<1 cm	21 (61.8)
>1 cm	13 (38.2)
Complications of IE	
Abscess and SOV aneurysm	5 (14.7)
Perforation	2 (5.8)
Systemic embolisation	5 (14.7)

[Table/Fig-3]: Valve involvement and complications.
SOV: Sinus of valsalva

Management protocol and outcome	Treatment duration	n (%)	Relapse n (%)
Management modality			
Medical	12 weeks	28 (82.4)	2 (7.1)
Urgent Surgery	<7 days	6 (17.6)	0
Antibiotic used			
Rifampicin+Doxycycline	12 weeks	8 (23.5)	2 (25)
Rifampicin+Doxycycline+gentamycin	12 weeks (gentamycin: 4 weeks)	18 (53.0)	0
Rifampicin+Doxycycline+co trimoxazole	12 weeks	8 (23.5)	0
Overall outcome			
Survived		28 (82.4)	
Death		(6)*	

[Table/Fig-4]: Management protocols and outcome.
*All patients had heart failure refractory to medical therapy- 2 patients underwent emergency surgery and 4 patients with multiorgan dysfunction were considered very high-risk for surgery in the acute phase and refused surgery

DISCUSSION

Brucellosis can present acutely, subacutely, or chronically [4]. Infective Endocarditis (IE), which can lead to degeneration of the native valve and heart failure if left untreated, is a major cause of mortality in

brucellosis [4]. Human brucellosis is often described as a disease with diverse manifestations [1]. Fever is almost always present in most patients [1,12], and in the present study, all patients had fever at presentation. The challenges associated with a microbiological diagnosis of brucellosis, even in the presence of valve vegetations, often result in delays, and several studies have reported a prolonged duration of fever associated with the disease [6,14,15]. The median duration of fever in the present study was one month, with the longest duration recorded being seven months. In a study by Keshtkar JM et al., the mean duration of symptoms was 99.7 days [15]. While fever is the most common symptom, it may not be present in all patients, as observed in the Gulhane study where 11.3% of patients did not have fever at presentation [16]. The presence of dyspnoea in brucellosis suggests possible cardiac involvement. Although brucellosis is known to cause reactive arthritis, joint pain can also occur in IE due to other organisms and has limited localising value [1]. In this study, 17.6% of patients reported a history of arthralgia. The bacteria has a tropism for the reticuloendothelial system, and the presence of lymphadenopathy can raise suspicion of brucellosis in a patient with IE; however, the incidence of clinically significant lymphadenopathy is low (7-10%) [1]. None of the patients in the present study had significant lymphadenopathy on physical examination. Splenomegaly was noted in 23.5% of the patients.

Haematological findings commonly seen in brucellosis include anaemia, mild leucopenia with relative lymphocytosis, and thrombocytopenia. In the present study, the majority of patients (61.1%) had a normal leucocyte count, with leucopenia observed in 14.7% of patients. The Gulhane study [16] also reported that the majority of patients had a normal leucocyte count (Mean: 6964.9/mm^3, Range: 2500-13100/mm^3). Leucocytosis was observed in patients who had complications of IE, such as perivalvular abscess and systemic embolism. Thrombocytopenia and pancytopenia are frequently seen in brucella infections [1] and were observed in 32.3% and 17.6% of patients, respectively. These findings have been attributed to hypersplenism and bone marrow involvement [1,14]. The presence of thrombocytopenia and pancytopenia in IE should raise a suspicion of brucellosis. Thrombocytopenia and pancytopenia normalised in all patients who showed clinical improvement with antibiotic therapy.

The laboratory diagnosis of brucellosis includes blood culture, serological tests, and nucleic acid amplification assays [10,11]. Brucella is a slow-growing, fastidious organism. With modern automated blood culture systems, the mean time for identification ranges from 3-7 days, and sometimes subculture growths have been identified as late as 20 days [11,12]. In the present study, Bact/Alert media was used for culture, and the mean duration of blood culture growth was 5.8 days. Brucella melitensis was isolated in all cultures. In cases of IE, especially when Brucella is suspected, it is advisable to incubate blood cultures beyond 7-10 days. Additionally, bone marrow cultures are recommended in cases with a strong suspicion due to Brucella's affinity for the reticuloendothelial system. For serological tests detecting antibodies, the diagnostic cut-off is a titer of >1:160 in non endemic areas and >1:320 in endemic areas [12]. In our study, a Standard Agglutination Test (SAT) was performed to detect antibodies, and the titers were >1:640 in all patients.

Brucella endocarditis can affect normal, damaged, and prosthetic heart valves [15,16]. In the present study, the majority of patients (64.7%) had underlying Rheumatic Heart Disease (RHD), 14.8% had prosthetic mechanical valves, and 17.6% had no pre-existing valve disease. Brucella endocarditis was observed in patients with no pre-existing valvular disease in 30.6% of patients in a study by Keshtkar JM et al., and in 39.6% in the Gulhane study [15,16]. The most commonly involved valve in Brucella endocarditis, as reported in the literature, is the aortic valve, with involvement ranging from 52-70% in most studies [15-17]. In this study, both the aortic and mitral valves were involved with equal frequency. The higher incidence of mitral valve involvement in the present study is due to the higher incidence of RHD in India, where mitral valve involvement is predominant. Brucella endocarditis is associated with large vegetations and systemic embolisation. Approximately one-third of patients in the present study had vegetations larger than 1 cm, and 14.7% of patients had systemic embolisation, including stroke and limb ischaemia. Aortic perivalvular abscesses have been frequently reported with brucellosis [15,16,18]. Five patients in the present study had an aortic perivalvular abscess, and one of them led to a sinus of Valsalva aneurysm. No significant conduction system abnormalities were noted in the present study.

The management of brucella endocarditis includes medical and surgical treatment based on the severity of valve involvement and complications [15-19]. In the present study, 82.4% of the patients were managed medically during the acute phase. Rifampicin (450-600 mg/24 h) and doxycycline (200 mg/24 h) were used in all patients for a total duration of three months. For patients with paravalvular complications, large vegetations, prosthetic valves, and those requiring surgery, additional Intravenous (i.v.) gentamycin was administered for four weeks. A few patients (23.5%) also received oral co-trimoxazole (960 mg/24 h) in addition to rifampicin and doxycycline, at the discretion of the treating physician. The number of patients in the present study is too small to compare the different antibiotic regimens. The ESC guidelines [9] propose using a combination of doxycycline, rifampicin, and cotrimoxazole for 3-6 months, and some authors recommend adding gentamycin for the first four weeks [15,16,19]. Relapse was observed in 2 (5.8%) patients. Both patients had received an oral antibiotic regimen of doxycycline and rifampicin for 12 weeks without any intravenous drug. The results of the Gulhane study [16] showed that mortality was lowest in patients who received i.v. aminoglycoside in addition to the oral regimen. A study by Jia B et al., also showed a lower relapse rate with the addition of quinolone or aminoglycoside [20]. Due to the lack of large series, the optimal duration of treatment is still unclear. Patients without complications or severe valve lesions can be managed medically alone [16,17,19].

In the present study, emergency surgery was performed on six patients in the acute phase of IE who had severe valve regurgitation, paravalvular abscess, and refractory heart failure not responding to medical treatment. The mortality rate associated with emergency surgery was 33.3%. Emergency surgery is reserved for patients with paravalvular complications or refractory heart failure that is not stabilised by medical management, and it carries a higher perioperative mortality compared to elective surgery [15-17]. Patients with significant valve lesions who were stabilised medically in the acute phase underwent elective surgery after six weeks. Elective surgery after completion six weeks of antibiotic therapy is preferred in such patients [15,17]. There was no mortality associated with elective surgery in the present study. All patients who underwent surgical treatment received four weeks of intravenous gentamycin during their hospitalisation in addition to oral antibiotics. Oral rifampicin and doxycycline were continued postoperatively to complete a total duration of three months. A review by Keshtkar JM et al., showed that combined medical and surgical treatment decreased mortality from 32.7% in the medical group to 6.7% in the combined surgical and medical treatment group [15]. A combined approach is necessary for patients with significant valve lesions to improve outcomes.

The meta-analysis by Narimisa N et al., reported a mortality rate of 26% for brucella endocarditis [3]. In the present study, the observed mortality rate was 17.6%. All patients in the study had heart failure with severe valve regurgitation. Two-thirds of these patients had multiorgan involvement, which deemed them very high-risk for surgery in the acute phase. One-third of the patients who died had undergone emergency surgery with valve replacement. Risk factors for mortality included refractory heart failure requiring surgery in the

acute phase and multiorgan dysfunction. Patients with prosthetic valve endocarditis in the present study did not experience any complications and were managed solely with medical treatment. A recent review demonstrated favourable outcomes in patients with brucella prosthetic valve IE when timely treatment was provided [21].

Limitation(s)

The limitations of the present study include a small sample size and a retrospective cohort design. Detailed data regarding contact with farm animals or animal products were not available. Additionally, information on antibody titers post-treatment during follow-up was not accessible. Despite these limitations, the current study contributes to the limited knowledge about Brucella endocarditis.

CONCLUSION(S)

Brucella endocarditis is frequently characterised by the presence of large vegetations and can lead to paravalvular and embolic complications. The presence of thrombocytopenia/pancytopenia with a normal or reduced leukocyte count in a patient with endocarditis should raise a suspicion of brucellosis. Prolonged incubation of blood cultures is necessary when there is a clinical suspicion. The addition of intravenous gentamycin to oral therapy may help decrease relapse rates.

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