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Clinical Spectrum of Brucellosis from a Tertiary Care Centre

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Authors' contributions

This work was carried out in collaboration between all authors. Author KP designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author SS managed the analyses of the study. Author KP managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Brucellosis is an under reported, emerging zoonotic disease with worldwide distribution, which is particularly endemic in many countries of the Mediterranean basin. We reviewed thirteen cases of culture proven Brucellosis and their clinical manifestations admitted at our Institute.

Materials and Methods: Medical records of thirteen cases of Brucellosis were reviewed between Jan 2013 to June 2017. Demographic data, clinical manifestations, clinical complications and outcome of these cases were analyzed.

Results: The age range of patients was between 26-57 years with a female preponderance (7 females and 6 males). All the patients had history of occupational exposure to cattle and they

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were hailing from rural areas (13/13). In 8 patients with Fever of unknown origin (FUO) fever was the main presenting symptom and the duration of fever was for more than 3 months with associated joint pains, headache and vomiting. Five patients had features suggestive of Infective Endocarditis (IE) with vegetation on Aortic valve. 13/13 cases were positive for Brucella culture. 5/13 cases positive for Brucella antibodies were also positive by culture. 8/13 cases were negative for Brucella antibodies.

Conclusion: Early diagnosis of brucellosis facilitates prompt therapy that helps in timely management of this Infectious disease with a successful outcome.

Keywords: *Brucella endocarditis; aortic valve; Brucella melitensis; zoonotic.*

1. BACKGROUND

Brucellosis is a worldwide zoonotic infection which is prevalent in western parts of Asia, Middle Eastern, Southern European, and Latin American countries [1]. Humans are infected by close contact with an animal, or by the consumption of meat or dairy products infected by Brucella. The global burden of human brucellosis remains to be more than 500,000 infections per year [2]. The three most frequent agents of human brucellosis are *B. melitensis*, *B. abortus*, *B. suis* and less frequently *B. canis* [3].

The most common causative agents of Brucellosis in India are *B. melitensis*, and *B. abortus*.

B. melitensis is the most virulent strain and currently accounts for most recorded cases globally with cattle emerging as an important reservoir [4].

The clinical spectrum of human brucellosis ranges from inapparent, asymptomatic infection to severe disease with life-threatening complications. Symptoms of brucellosis are usually non-specific and include fever, sweating, malaise, weight loss, fatigue, headaches, arthralgia and myalgia. Osteoarticular manifestations are the most frequent focal complications, often affecting the spine and sacroiliac joints followed by pneumonia, meningitis and endocarditis. Usually Brucellosis patients present with pyrexia associated with backache and joint pains and a high degree of early clinical suspicion about the disease and adequate management is essential for the diagnosis [5]. The incidence rate of brucellosis in patients of Fever of unknown origin is 132.4 per 100,000 cases [6].

Cardiac involvement comprises an important complication of brucellosis and is responsible for up to 80% of *Brucella*-related deaths [7] although *Brucella endocarditis* itself occurs in only 1–2% of all cases [1]. In *Brucella endocarditis*, aortic

valve involvement is frequently observed and endocarditis is the most common cause of death [8,9].

We present 13 case series of Brucellosis to create awareness regarding the disease in specific clinical situation, particularly in the persons belonging to high risk category for Brucellosis and to look into various clinical manifestations and discuss them along with a review of the published literature on brucellosis. We reviewed eight cases of Brucellosis which presented as Fever of unknown origin (PUO) with fever and joint pains as the major clinical manifestation and 5 cases of *Brucella endocarditis*.

1.1 Objective

To review the demographic, clinical complications, laboratory findings and outcome of Brucellosis in our case series.

2. MATERIALS AND METHODS

Medical records of thirteen cases of culture proven Brucellosis and their clinical manifestations were reviewed, admitted at our Institute between Jan 2013-June 2017. From each patient 2 sets of blood cultures were collected within 24 hours, 10 ml each in Standard (SN) and FAN (FN) plus aerobic blood culture bottles and incubated in BacT/Alert 3D continuous monitoring blood culture system. (CMBCS).

Isolates were identified by Vitek 2C system using Identification by Gram negative (ID GN) panel. Serological diagnosis of brucellosis was done by standard tube agglutination test.

2.1 Microbiological Workup

In our laboratory, *Brucella melitensis* was isolated from 2 sets of Blood cultures within 3 days (average) from each of these patients by using BacT/Alert FAN Plus and Standard aerobic

bottles (*bioMerieux, France*). Positive Blood cultures and aortic valve tissue was subcultured on blood agar and chrome agar and incubated in a 5% carbon-dioxide generating pouch at 37°C for 48 hours. Grey white pin point moist non haemolytic colonies were observed on both media after 48 hours. (Fig. 1) Grams stain of colonies showed Gram negative coccobacilli. (Fig. 2) The isolates were identified by Vitek 2C system (*bio Merieux, France*) using ID GN panel. The time to detection for *Brucella* species is 5-7 days on an average. Any negative blood culture bottles, in a clinically suspected case of brucellosis, is unloaded from the system after 5 days and further incubated at ambient air in the incubator at 37°C for another 7-10 days. A terminal subculture is done on 5% sheep blood agar incubated at 37°C under 5% CO₂ for 48 h. All positive cultures are identified using the Vitek 2C system (*bio Merieux*) and the ID GN panel. Antibiotic susceptibility is not routinely indicated, due to lack of resistance plasmids and thereby rare development of antibiotic resistance. Standard tube agglutination was done for all the cases for detection of *Brucella melitensis* antibodies.

3. RESULTS

The age distribution of our cases was between 26-57 years (6 males). Majority were in the age group of 51-60 years. All our patients (13/13) were farmers and had history of occupational exposure to cattle who were hailing from rural areas. Eight cases presented as F.U.O and five cases presented as *Brucella Endocarditis*. In F.U.O and *Brucella Endocarditis* cases the duration of fever varied (Table 1) Fever and chills with rigors were the main presenting symptoms in our study followed by other symptoms (Table 2). Trans oesophageal echocardiography

(TEE) was done in 6/13 cases where vegetations were seen in 5/13 cases. 13/13 of our cases were positive by culture. 5/13 (38.4%) cases were positive by serology and culture. 8/13 (61.5%) cases were negative by serology and positive by culture. We adopted tube agglutination test where 1: 160 is considered to be the cut off. Serological titres of *Brucella* antibodies ranged from 1:160 to 1:1280 (Table 3) All 5 patients had elevated titers which were in diagnostic range. Later after 6-8 weeks of therapy serum antibody titres were repeated where an antibody titre of <1:160 titres were considered as cured.

Table 1. Duration of fever in PUO & Endocarditis cases

Fever duration in PUO cases (n=8)	Fever duration in IE cases (n=5)
4 months (n=1)	2 months (n=3)
1 month (n=3)	6 months (n=1)
10 months (n=1)	20 days (n=1)
2 months (n=1)	
25 days (n=1)	
5 months (n=1)	

In 2 cases with Infective Endocarditis, surgical procedure aortic valve replacement (AVR) was done and *Brucella melitensis* was also isolated from aortic valve tissue and blood cultures and were treated successfully with doxycycline in combination with Gentamicin for 6-8 weeks during the hospital stay and post operative antibiotic therapy continued for a period of 6 months after discharge from the hospital. And other 3 cases though didn't undergo surgery were treated for 6-8 weeks All our F.U.O cases were treated with doxycycline in combination with Streptomycin for 6-8 weeks with a successful outcome. There was no mortality recorded in our case series.

Table 2. Clinical manifestations of brucellosis

Clinical manifestations	Number n =(13)	Percentage (%)
Fever	13	100
Chills & rigors	7	53.8
Joint pains	2	15.3
Sudden onset of breathlessness(SOB)	3	23.07
Cough	4	30.76
Chest pain	3	23.07
Vomiting	2	15.3
Headache	5	38.4
Backache	2	15.3
Splenomegaly	1	7.69
Hepatomegaly	1	7.69
Lymphadenopathy	1	7.69



Fig. 1. Colony morphology of *B. melitensis* on Blood agar and Chrome agar plates with grey white pin point shiny moist non haemolytic colonies

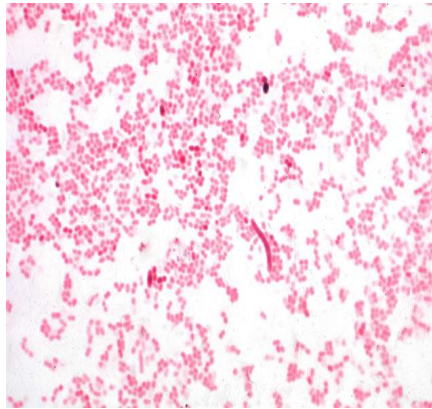


Fig. 2. Grams stain of colonies showing gram negative coccobacilli

Table 3. Serological titres of Brucella antibodies

Serological titre	Number
1:160	1
1;320	2
1:640	1
1:160	1

4. DISCUSSION

Brucella is an emerging potential bio-threat pathogen with public health importance [10]. As a

biosafety level three organism, suspected Brucella spp. should be handled with personal protective equipment (PPE) that includes protective laboratory clothing, gloves, face and eye protection and respiratory protection [11] Brucellosis is a bacterial disease transmitted to humans by consumption of infected, unpasteurized animal milk or through direct contact with infected animals, particularly aborted fetuses [12].

The pathogenic species of Brucellosis are *B. melitensis*, *B. abortus* and *B. suis*. *B. suis* is rarely found in 5% cases. In all our cases *B. melitensis* was isolated from culture which remains a gold standard test [3].

This disease is more common in rural areas. All our patients were also hailing from rural areas similar to Mohan et al. study [13]. Brucellosis is a protean disease with multi-systemic involvement. Misdiagnosis and delay in treatment leads to complications like bone and joint involvement, endocarditis, meningitis, pneumonia and epididymo-orchitis [14].

Female preponderance in our study was probably because of direct contact with animals while handling them for milk which was found to be significantly most important pre-disposing factor with all our cases.

Serological diagnosis of brucellosis was based on demonstrating antibodies for *B. melitensis* in significantly high titer ($\geq 1:160$) against Brucella antigen by standard tube agglutination test. (SAT) SAT remains the most popular and yet used worldwide diagnostic tool. SAT measures the total quantity of agglutinating antibodies (IgM and IgG) SAT titers of 1:160 or greater are considered diagnostic in conjunction with a compatible clinical presentation [14]. Titers are useful for monitoring the treatment. In our study serologically negative and culture positive cases were 61.5%.

Cardiovascular complications of Brucellosis include endocarditis, myocarditis, pericarditis, aortic root abscess, thrombophlebitis with pulmonary aneurysm and pulmonary embolism.

Brucella endocarditis constitutes a rare but severe complication of brucellosis and most cases described in the literature are single reports or small series. It is observed in less than 2% of brucellosis cases, responsible for up to 80% of deaths [15]. It may occur on previously normal valves and most commonly affected is the aortic valve in 75% of the cases as similar in our cases. Diagnosis of *Brucella endocarditis* can be made with history, clinical findings, echocardiographic images confirming the diagnosis of infective endocarditis, isolation of the agent from tissue samples, positive agglutination test. Increased diagnostic and therapeutic vigilance is required for timely and efficient treatment of *Brucella endocarditis*.

In our study *Brucella endocarditis* was confirmed by TEE, by blood cultures, after surgery from excised aortic valve tissue and also by serological testing for Brucella antibodies.

Despite adequate medical therapy, *Brucella endocarditis* generally requires urgent or emergency cardiac surgery with the replacement of the affected valve in combination with conservative management for a large period of time, are deemed necessary for the successful treatment usually, because of the inability to control the infectious process with progression to a medically uncontrollable congestive cardiac failure. On the other hand, the microbe causes tissue destruction, with a tendency for progressive ulceration and significant risk of embolism [9].

However, in a recent report Cohen et al. described one case and found another 12 in the

literature, which were cured by antibiotic therapy alone [16]. Fifteen well documented patients were cured by medical treatment alone in another study [17]. We treated 3 cases of *Brucella endocarditis* with conservative management alone.

But in the majority of cases surgery is indicated by failure of adequate conservative therapy for a reasonable period of time in the presence of an hemodynamically significant valve lesion.

Surgery was planned and tab augmentin 1.2 mg IV 12th hrly was started prophylactically the same day before surgery was done. Urgent aortic valve replacement was done with 23 mm SJM non rotatable valve for congenital rheumatic heart disease (CRHD), severe AR, post IE.

Also, the antibiotic schemes have varied from single to triple therapy, but most authors believe that single antibiotic therapy must be avoided because the development of resistance has been frequently demonstrated in this situation. Generally, rifampicin and/or co-trimoxazole must be added to the classic doxycycline in dosages usually higher than those recommended for other infections [18].

The other serological parameters such as Widal, Dengue, Weil Felix, Leptospirosis and Malaria were tested to rule out FUO in our cases, since fever was continuous inspite of empirical treatment. As Human brucellosis is found to have a significant presence in rural areas where people live in close association with animals, henceforth occupational history was elicited for all the 13 cases hailing from rural areas and who had close contact with animals while taking the herds to the fields as a farmer. Probably these were the likely reasons that triggered for sampling by the clinicians with a suspicion of brucellosis.

As brucellosis is an intracellular infection treatment should be administered for six weeks or longer as 30 days or less results in an increased relapse rate, even with the more potent doxycycline-streptomycin regimen. All eight cases of FUO were treated with Tab doxycycline 100 mg BD for 6 weeks in combination with Streptomycin 750 mg IM for 5 days in a week for 3 weeks.

The World Health Organization (WHO) issued recommendations for the treatment of human brucellosis in 1986 [8], suggesting the use of

doxycycline, 100 mg twice daily for six weeks combined with either rifampicin, 600–900 mg daily for six weeks, or streptomycin, 1 g daily for 2–3 weeks [19].

All five cases of *Brucella*. Endocarditis was treated successfully with Tab doxycycline P.O (per oral) 100 mg BD for 6 weeks in combination with Gentamicin 80 mg IV 8th hourly for 3 weeks and all were discharged under stable condition with a successful outcome.

These five patients were followed-up at regular intervals for the next 6 months. For the two cases which have undergone aortic valve replacement the postoperative antibiotic therapy was continued for a period of 6 months. No relapses occurred during the six month follow-up period of the patient.

The literature shows considerable variation in the duration of the antibiotic therapy after surgery, varying from 2 weeks to more than 1 year. However, there is some consensus about the need to prolong the treatment for at least 3 months post-surgery [20]. Even in our cases emergency surgery was done without any complications.

Congestive heart failure is responsible or the majority of deaths in *Brucella endocarditis* [21]. Our patients were treated successfully and there was no mortality documented in our cases.

5. CONCLUSION

Cases presenting as Fever of unknown origin associated with backache and fever should alarm the clinician to have high degree of suspicion towards Brucellosis. Establishing a history of travel to endemic countries and also exposure history to animals and/or their products is crucial in order to alert the clinician for early diagnosis of Brucellosis and facilitate prompt therapy that helps in timely management of this Infectious disease with a successful outcome.

Brucella endocarditis, is a rare entity of Brucellosis. For the timely and efficient treatment it is always necessary to proceed with immediate surgical treatment by replacement of the affected valve, if there is increase in size of the vegetation or development of abscess in the valve, hemodynamic instability followed by. antibiotic treatment for a prolonged period of time is deemed necessary for successful treatment of *Brucella endocarditis*. There was no evidence of

recurrence of infection in any of our patients during a period of 6 months follow up. Though *Brucella endocarditis* is known for large vegetations and surgery is the treatment of choice, our cases showed that initiation of early treatment besides life saving can restore the affected valve anatomy to minimal stigmata.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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