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Clinical profile of brucellosis from a tertiary care center in southern India

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ABSTRACT

Objective: To highlight the spectrum of clinical manifestations, labs, complications, treatment and outcome of brucellosis. **Methods:** Retrospective study was conducted in Kasturba Medical College, Manipal University, Karnataka, India which included 68 confirmed cases of brucellosis from January 2006– April 2010. Diagnosis of brucellosis was made by culturing the sera/body fluids by standard BACTEC method (or) by testing the sera for *Brucella* agglutinins using the standard agglutination test (SAT). A titer of 1:320 or more was considered as significant. SPSS 16 was used for statistical analysis and Microsoft Excel for graphical representation. **Results:** Of the 68 patients, 46 (68%) were male and 22 (32%) were female patients with age distribution of 9–75 years. Forty four (64.7%) had history of contact with unpasteurized dairy products or infected animals. Symptoms included fever (68, 100%), myalgia (21, 31%), musculoskeletal symptoms (23, 34%), headache (16, 24%), gastrointestinal symptoms (19, 28%) and altered sensorium (3, 4%). Co-morbidities and associations included HIV positivity (2, 3%), type 2 diabetes mellitus (13, 19%), steroid therapy (3, 4%) and HBsAg positivity (8, 12%). Ten (15%) patients had cervical lymphadenopathy, 4(6%) had splenic enlargement, 6 (7%) had hepatomegaly, 19 (28%) had hepatosplenomegaly and 2(3%) got meningeal signs. Anaemia was observed in 39 (57.3%) cases, high erythrocyte sedimentation rate (ESR) was present in 55 (80.8%) cases, leucocytosis in 10(14.7%), leucopenia in 10(14.7%), thrombocytopenia in 23 (33.82%) and thrombocytosis in 2 (2.94%) cases. **Conclusions:** In countries like India, where brucellosis and tuberculosis are endemic; rapid, sensitive and highly specific diagnostic methods are required to make early diagnosis and prevent resistance as there is an overlap in therapy.

1. Introduction

Human brucellosis is the commonest bacterial zoonosis worldwide^[1] with an indolent course quite prevalent in the developing countries including India. It is classified as a Class B Bioterrorist agent^[2] and is one of the highly neglected tropical diseases. It masquerades multiple infectious and non infectious conditions causing a significant diagnostic dilemma^[3]. Since India is endemic for tuberculosis, there is always an overlap in the clinical symptomatology and treatment. Moreover, the surveillance of this organism is not practised regularly and hence the true incidence of the disease is not known. It is under

diagnosed, underreported and is probably tip of the iceberg^[3]. The exact burden of this problem is not known in India because of paucity of reports and the disease being misdiagnosed as other conditions. Moreover, there are hardly any studies in India, which have specifically looked at laboratory parameters and its clinical correlation.

2. Materials and methods

This retrospective study was undertaken in Kasturba Medical College, an affiliate medical school of Manipal University, Karnataka, India. Kasturba Hospital in Manipal, India is a 1560 bedded tertiary care university hospital in southern India. The medical records at Kasturba Hospital, Manipal, India were accessed and all consecutive cases from January 2006 to April 2010 with the diagnosis of human brucellosis as per the International Classification of Diseases codes were included in the study. Diagnosis of

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brucellosis was made by culturing the sera/body fluids on standard BACTEC method^[3] (or) testing the sera for brucella agglutinins using the standard agglutination test (SAT). A titer of 1:320 or more was considered as significant^[4]. Standardised chart abstraction form was used to obtain baseline demographic data, predisposing factors, clinical features, laboratory data, treatment details and outcome. SPSS 16 was used for statistical analysis and Microsoft Excel for graphical representation.

3. Results

Out of 68 patients, 46 (68%) were males and 22 (32%) females with age distribution in the range of 9 –75 years. Patients mainly presented with fever as the predominant symptom in 68 cases (100%). The other symptoms were myalgia (21, 31%), musculoskeletal symptoms (arthralgia, backache) (23, 34%), headache (16, 24%), gastrointestinal symptoms (nausea, vomiting, diarrhoea, constipation and pain abdomen) (19, 28%) and altered sensorium (3, 4%). In the present study, 44 (64.7%) cases showed history of contact with unpasteurized dairy products or infected animals. Co-morbidities and associations included HIV positivity (2, 3%), Type 2 Diabetes mellitus (13, 19%), steroid therapy (3, 4%) and HBsAg positivity (8, 12%). On physical examination, cervical lymphadenopathy was shown in 10 cases (15%), splenic enlargement in 4(6%), hepatomegaly in 6 (7%), hepatosplenomegaly in 19 (28%) and meningeal signs in 2(3%). The haematological abnormalities included anemia (<10 g %) in 39 (57.3%) cases, high erythrocyte sedimentation rate (ESR) (>50 mm at the end of one hour) (55, 80.8%), leucocytosis (>11 000/cumm) (10, 14.7%), leucopenia (<4 000/cumm) (10, 14.7%), thrombocytopenia (<1.5 lakh/cumm) (23, 33.82%) and thrombocytosis(>4l akhs/cumm) in 2(2.94%) cases. Brucellosis was diagnosed by culturing sera/body fluids on BACTEC (or) by standard agglutination test (SAT) for brucella agglutinins. A titer of 1: 320 was considered as diagnostic standard of brucellosis which was positive in 61 (90%). Fifty (74%) had BACTEC blood, 2 (3%) had CSF and 3 (4%) had bone marrow growing brucella. Six patients (8.82%) were given empirical anti tuberculosis therapy as there was a diagnostic dilemma and the symptoms, signs and labs simulated tuberculosis. The different treatment regimens employed in our patients included a combination of doxycycline and rifampicin in 3 (4%) cases or doxycycline, rifampicin and aminoglycoside (streptomycin/gentamicin) in 17(25%) cases or doxycycline and aminoglycoside in 48(71%) cases. Complications included endocarditis (2, 3%), orchitis (2, 3%), neurobrucellosis (3, 4%), and death (1, 1.47%).

There was a patient presenting with chronic meningo encephalitis with hydrocephalus masquerading as tubercular meningitis who improved with therapy. A 30 year old lady presenting with spinal epidural abscess with vertebral osteomyelitis according to magnetic resonance imaging (MRI) (Figure 1). A 45 year old lady in this study had endocarditis with vegetation on the right coronary cusp of the bicuspid aortic valve and responded to medical therapy (Figure 2).

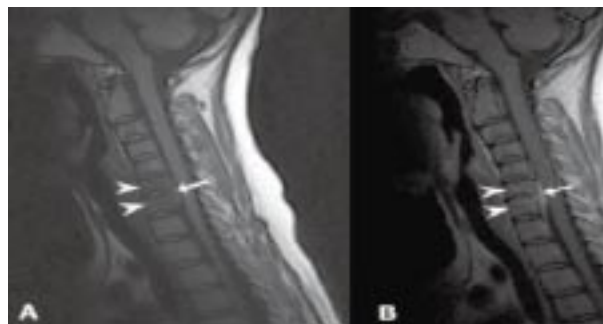


Figure 1. MRI in a 30 year old female showing spinal epidural abscess with vertebral osteomyelitis (A:T1W sagittal , B: post contrast).

Section of cervical spine showing an epidural abscess (←) compressing the spinal cord at C6–C7 level with associated hypointensity of the involved vertebra suggestive of spondylodiskitis.



Figure 2. Echocardiographic photograph revealing vegetation on the right coronary cusp of the bicuspid aortic valve.

4. Discussion

Brucellosis is caused by the facultative gram negative bacteria belonging to the genus *Brucella*. Brucellosis is the commonest anthrozoonotic infection with a pandemic distribution^[1] and remains an uncontrolled problem in regions of high endemicity such as Mediterranean, Middle East, Africa, Latin America and parts of Asia. It has earned its name as a great imitator alongside tuberculosis and syphilis as it mimics multiple infectious and non infectious pathologies. Human infection can occur through consumption of unpasteurised dairy products and raw meat which may contain the bacteria. Infection can also occur through skin abrasions and inhalation of airborne animal manure. Occupational exposure of veterinarians and laboratory personnel can result in transmission of the disease through contaminated aerosols^[5, 6]. The disease can present as an acute febrile illness but also has a tendency towards chronicity and persistence, becoming a granulomatous disease capable of affecting any organ system ^[7]. The timely and accurate diagnosis of human brucellosis continues to challenge clinicians because of its non-specific clinical features, slow growth rate in blood cultures, and the complexity of its serodiagnosis ^[8].

Most of our patients in this study were agriculturists and from a rural base which has also been cited in other studies

by Mantur *et al.*[6,9] Human brucellosis affects all age groups and our study also revealed a wide range of age distribution between 9 and 75 years. The mean age with brucellosis in our study was 40 years as has been described in other studies [10].

This reflects the magnitude of the socio-economic impact of brucellosis in endemic areas like India, as it affects mainly the most productive group in the population. Male preponderance 46 (68%) in our study is probably because of constant close contact with livestock during outdoor agricultural activities and milking the cows. This observation has also been seen in studies by Kochar *et al* in Bikaner[9]. Forty four (64.7%) gave history of contact with infected animals or ingestion of unpasteurised dairy products which may have resulted in the transmission of the disease [6,10].

14 % of the patients presented with fever < 1 week, 23% with fever of 1–4 weeks and 63% with fever of > 4 weeks. This suggests that more than 50% had a chronic presenting complaint which was also seen in other comparative studies in India and worldwide [9,12].

The commonest presenting symptoms include fever (68, 100%), myalgia (21, 31%), musculoskeletal symptoms (arthralgia, backache) (23, 34%), headache (16, 24%), gastrointestinal symptoms (nausea, vomiting, diarrhoea, constipation and pain abdomen) (19, 28%) and altered sensorium in 3 (4%). In a study by Kokoglu *et al.*[12] out of 138 patients, 108 (78.3%) had fever, 107(77.5%) had arthralgia and 98 (71%) presented with constitutional symptoms. Mantur *et al*[6], in 2006 studied 495 patients and 417 (84.2%) had fever, 117(23.6%) had arthralgia and 6 (1.2%) had constitutional symptoms. In our study, 4 (6%) had splenic enlargement, 6 (7%) had hepatomegaly and 19 (28%) had hepatosplenomegaly. 37 (26.8%) had hepatomegaly and 50 (36.2%) splenomegaly in a study done by Kokoglu *et al.*[12]. There have been no reported studies in India to the best of our knowledge which have highlighted the laboratory parameters, especially the haematological profile.

In our study, anaemia was present in 39 (57.3%) cases, leuopenia in 10(14.7%), leucocytosis in 10 (14.7%), thrombocytopenia in 23 (33.82%), thrombocytosis in 2 (2.94%) and elevated ESR in 55 (80.8%). A higher proportion of our patients had anemia. This could be due to the chronicity of infection in 63% of the patients and rural base with low socio economic status (concomitant nutritional anemia and iron deficiency due to hook worm infestation). In Hasanjani Roushan *et al*[13] study on 469 patients, 71 (15.1%) had anemia, 14 (3.0%) had leucopenia, 57 (12.2%) had leucocytosis, 16 (3.4%) had thrombocytopenia, 5 (1.1%) had thrombocytosis and 365 (77.8%) showed elevated ESR.

The associated illnesses included HIV in 2 cases (3%). The association of brucellosis with HIV had been reported in case reports earlier. The clinical presentation, diagnosis, response to therapy and outcome are similar to those observed in non-HIV infected patients [14].

In addition, other immunocompromised states like type 2 Diabetes mellitus (13, 19%), steroid therapy (3, 4%) and HBsAg positivity in 8 cases (12%) were observed in our study [15].

Brucellosis was diagnosed in our study by culturing sera/body fluids on BACTEC[16] or by standard agglutination test (SAT) for brucella agglutinins. A titer of 1: 320 was considered diagnostic of brucellosis[4]. Several studies have shown that blood culture is the gold standard in the diagnosis of brucellosis. The conventional method for

the isolation of *Brucella* spp. from clinical specimens has been replaced by automated culture systems—which has a higher sensitivity and aids in early diagnosis[17,18]. The lysis centrifugation can have a sensitivity of 90% in acute and 70% in chronic cases. Our study also showed a sensitivity of 80.8% for isolation of *Brucella* spp. by BACTEC method [18, 19].

Bone marrow cultures may provide a higher sensitivity, yield faster culture times, and may be superior to blood cultures when evaluating patients with prior antibiotic use [20].

Brucella can also be cultured from body fluids such as CSF as seen in our study where 2 (3%) and 3 (4%) cases were isolated from CSF and bone marrow [20].

When culture facilities are unavailable, the diagnosis of brucellosis depends on the serum agglutination test. In endemic areas, high background values could occur that may affect the diagnostic value of the test [4]. Hence we considered a higher cut off of 1: 320 for the diagnosis [6]. The specificity and positive predictive value of a positive test result could be increased by selecting a higher cut-off value for areas where brucellosis is endemic. Mantecon *et al*[4] in their study showed a sensitivity of 84.6% on standard agglutination test at any titer in patients with culture proven brucellosis as compared to 86% in the our study [21].

Complications in our study included neurobrucellosis (3, 4%), endocarditis (2, 3%), orchitis (2, 3%), and death (2, 3%). In a study done by Kochar *et al* [9], out of 175 cases, 1 had endocarditis, 33 neurobrucellosis and 5 orchitis. Neurological complications can include peripheral neuropathies, chorea, meningoencephalitis, transient ischemic attacks, psychiatric manifestations, and cranial nerve palsy. In a series of 305 patients with brucellosis from Turkey, 20 (6.6%) patients presented with neurological involvement compared to 3 (4%) in our study [22]. We reported a patient presenting with chronic meningo encephalitis with hydrocephalus masquerading as tubercular meningitis who improved with therapy. First case of neurobrucellosis associated with hydrocephalus was described by Gunney *et al* in 2008 after consumption of fresh sheep cheese, stressing the need to consider neuro brucellosis in any case of hydrocephalus, especially in endemic areas of brucellosis with hydrocephalus [23,24].

A 30 year old lady presenting with spinal epidural abscess with vertebral osteomyelitis which has been reported as a rare complication seen in 0.1% of brucellosis cases was observed in this study. Magnetic resonance imaging (MRI) has become a powerful aid in investigating bone and soft tissue lesions in brucellosis [25].

The incidence of cardiovascular complications in brucellosis, such as endocarditis, myocarditis or pericarditis, is reported to be as low of 1% of cases [26]. In cases of endocarditis, which is the most common cardiovascular involvement of the disease, the aortic valve and less frequently the mitral valve are affected. No good response to medical therapy has been observed, and there is poor prognosis without surgery [26–28]. A 45 year old lady in our study had endocarditis with vegetation on the right coronary cusp of the bicuspid aortic valve and responded to medical therapy [29]. In our study, 2 (3%) patients had epididymo-orchitis which has also been seen with a similar incidence in the study done by Kochar *et al* in Bikaner, India [9]. One of our patients succumbed to the illness and it was a case of fatal myocarditis [30].

WHO issued recommendations for the treatment of human

brucellosis in 1986, 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. The Ioannina recommendations were developed in November 2006 and this included gentamicin as an alternative to streptomycin in combination with doxycycline. It also included sulphamethoxazole–trimethoprim (TMP–SMX) and quilone regimens [31,32]. We followed the WHO and Ioannina recommendations and there was no relapse or failure with the use of these guidelines.

Six (8.82%) of our patients received empirical anti tuberculosis therapy as the clinical presentation and labs revealed a diagnostic dilemma [3, 9, 23]. Since the two infections have a significant overlap in therapy, accurate diagnosis is the need of the hour to prevent resistance to rifampicin.

Brucellosis is a neglected tropical disease with unusual clinical manifestations requiring timely and accurate diagnosis to prevent morbidity and mortality.

In countries like India, where brucellosis and tuberculosis are common, there is urgent need to develop rapid, reliable, highly sensitive and easy to perform automated systems to detect brucella species to prevent streptomycin and rifampicin resistance (in view of treatment overlap). We found an association of brucellosis and hepatitis B in this study. Hence further studies are required to correlate this relationship. Though India is endemic for brucellosis, further studies are required to know the true incidence in the population. Routine serological testing for brucellosis in patients with prolonged febrile illness is required in endemic countries. Prevention depends on control of disease in animal hosts, effective heat treatment of dairy products, hygienic precautions and effective vaccines.

Conflict of interest statement

We declare that we have no conflict of interest.

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