ARE WE SEEING THE TIP OF AN ICEBERG? A FIVE YEAR STUDY OF HUMAN BRUCELLOSIS FROM A TERTIARY CARE HOSPITAL IN BANGALORE
Vijayashree Thyagaraj1, Tharanath Shankar2, Sujatha K.J3, Ronak Ajmera4

1Associate Professor, Department of General Medicine, Ramaiah Medical College and Hospital, Bangalore.  
2Senior Resident, Department of General Medicine, Ramaiah Medical College and Hospital, Bangalore.  
3Senior Resident, Department of General Medicine, Ramaiah Medical College and Hospital, Bangalore.  
4Junior Resident, Department of General Medicine, Ramaiah Medical College and Hospital, Bangalore.

ABSTRACT

BACKGROUND
Brucellosis is a common zoonotic disease that exists worldwide. In India where agriculture is the predominant occupation, people are exposed to livestock and are prone to be infected. The non-specific symptoms that overlap with other diseases make it difficult for the clinician to diagnose, apart from the patient himself presenting late due to mild, non-aggressive symptoms.

Brucellosis can also present as a well localized infection. There are not many studies from India focusing on the clinical presentation or other unusual manifestations of the disease and hence the need for this study. The aim of the study was to evaluate the protean manifestations of Brucellosis with special emphasis on organ / localized involvement and to analyze the various lab parameters and treatment practices.

MATERIALS AND METHODS
This was a retrospective study done during 2012 to 2016 at MS Ramaiah Medical College and Hospitals, Bangalore. Patients diagnosed with brucellosis during this period were included in the study. Their records were analysed for information regarding history, occupation, clinical features, investigations, treatment received and course in the Hospital.

RESULTS
Records of sixteen patients were selected and studied. The average age of the subjects was 47.75 ± 16.5 years. There were 13 (81.25%) male and 3 (18.75%) female patients. There was history of occupational exposure among 8 (50%) patients. All subjects had history of fever. Ten (62.5%) had musculoskeletal symptoms. Neurological manifestations were present in 5 (31.25%) subjects. Abdominal examination revealed hepatomegaly (n=2, 12.5%), splenomegaly (n=5, 31.25%), hepatosplenomegaly (n=1, 6.25%) and in one (6.25%) patient ascites. Two (12.5%) patients presented with multiple organ involvement. Blood investigations revealed anemia in 13 (81.25%), thrombocytopenia in 9 (56.25%) and elevated ESR in 7 (43.75%) patients. There were eleven (68.75%) patients with an abnormal LFT. Chest X ray was abnormal in 5 (31.25%) patients. Mean Brucella IgM titre was 4.18 ± 3.46 IU/ml. Different treatment protocols were followed. All patients recovered except for one who expired.

CONCLUSION
Brucellosis may present with multiple non-specific symptoms and signs or with localized organ involvement, often confusing the treating physician. A high index of suspicion is necessary to diagnose this condition.

KEYWORDS
Brucellosis, Organ Involvement, Treatment, Unusual Manifestation.


BACKGROUND
Brucellosis is a common bacterial zoonosis prevalent in many parts of the world like the Mediterranean basin, Middle East and parts of Asia. Data regarding incidence and prevalence of human disease in India is limited.

Human disease is most commonly caused by Brucella melitensis followed by B. abortus and B. suis. Brucellosis causes more than 500,000 infections per year worldwide. It is known by various names such as Mediterranean fever, undulant fever, Malta fever and gastric remittent fever.

Brucella were first discovered in 1887 in a patient in Malta and are small, non-motile, gram negative intracellular coccobacilli. The primary hosts are animals such as sheep, goat, camel and cows. Man is an accidental host. The disease is common in people from agrarian background who handle infected animals or consume unpasteurised dairy...
products or poorly cooked meat. It can also spread through unusual routes like sexual contact and inhalation.6

Brucellosis commonly causes symptoms of fever, musculoskeletal pain, fatigue, vomiting and malaise. Specific organ involvement such as endocarditis, neurobrucellosis and orchitis can occur though less commonly.7,8 In fact clinical manifestations are protean and the disease can be a great mimicker of other diseases.9,10

Musculoskeletal involvement is a common form of the disease with 2%-65% of cases being involved. Arthritis, bursitis, tenosynovitis and sacroilitis are more common in younger individuals and spondylodiscitis is more common in older individuals. These may lead to complications such as neurobrucellosis.5

Neurological manifestations can occur in the form of encephalitis, meningoencephalitis, brain abscess, cranial neuropathy, subarachnoid haemorrhage, myelopathy, radiculopathy, peripheral neuropathy and psychiatric symptoms.11 The frequency of neurological involvement is 5%-7% according to a review on the disease.12 Neurobrucellosis can leave behind neurological deficits such as aphasia, hearing loss and hemiparesis.13

Pulmonary involvement in Brucellosis is also very rare with four patterns of involvement namely pneumonia, pleural effusion, interstitial pattern and pulmonary nodules. Clinical and radiological manifestations are non-specific and difficult to differentiate from other common conditions.14

Brucella endocarditis is another rare complication occurring in 1%-2% of cases but has a high mortality of over 50%.15 Pericarditis may be another form of cardiac presentation.

Gastrointestinal presentation may be in the form of ileitis, enterocolitis or gastroenteritis.36

Haematological manifestations include anaemia and leukopenia and less commonly thrombocytopenia or pancytopenia.17 Hemophagocytic lymphohistiocytosis has also been described in some patients.18

Hepatosplenomegaly is also commonly seen and is taken as a clinical correlate of reticuloendothelial activity.17

Genitourinary complications may occur in 2-20% of cases and include epididymo orchitis, prostatitis and testicular abscess.19 In pregnant women brucellosis may cause spontaneous abortion. Other complications in women include cervicitis, salpingitis and pelvic abscess.20

Other rare organ involvement reported in literature are the kidneys (in the form of haematuria, proteinuria, renal failure, renal brucellosa and pyelonephritis),21 pancreatitis, thyroiditis, liver brucellosa, psoas abscess, gluteal abscess, breast abscess and splenic abscess.

Mortality is uncommon and usually is due to endocarditis or central nervous system involvement.22

Diagnosis is suspected in the background of possible exposure to Brucella organisms. It is confirmed by various tests such as culture, serological tests such as standard agglutination tube (SAT) test, indirect fluorescence antibody (IFA) test, anti-human globulin test and enzyme-linked immunosorbent assay (ELISA). Polymerase chain reaction technique is highly sensitive and specific but is expensive and not widely available.10

The gold standard of treatment for brucellosis with non-focal disease is with streptomycin 0.75-1 gm per day for 14-21 days along with doxycycline 100mg twice a day for 6 weeks. Streptomycin may be substituted with other aminoglycosides such as gentamycin. The WHO recommends doxycycline 100mg twice a day with rifampicin 600-900mg per day for 6 weeks or streptomycin substituted for rifampicin for 2-3 weeks. Complicated or localised disease such as endocarditis and neurological involvement is treated with triple drugs (aminoglycoside +tetracycline +rifampicin) for 3-6 months. Ceftriaxone and or fluoroquinolone may also be supplemented with this regimen.23,24

MATERIALS AND METHODS
This was a retrospective observational study done between 2012 and 2016 at M S Ramaiah Medical College and Hospitals.

Based on a study conducted earlier by Dr Mohan D K and Dr. Dhananjaya M in North Karnataka, with a relative precision of 25% and a desired confidence level of 95%, it was estimated that a minimum of 15 subjects needed to be included in the study.25

Data was retrieved using ICD coding for brucellosis from the medical records section and patients aged 14 years and above were included for data analysis.

All records were studied and information was collected with respect to history of presenting symptoms, place of residence, occupation history, clinical signs, investigations done and treatment given. Special attention was paid to specific organ involvement. Serum Brucella IgM and occasionally IgG antibody titres were checked using enzyme immunoassay (EIA) in the microbiology lab. Reference values were as follows: negative < 0.8, borderline 0.8 – 1.1, positive > 1.1.

Treatment given and course in hospital was recorded.

Data was analyzed using SPSS 16. Descriptive data was represented by percentages. Quantitative parameters such as age, lab parameters were described in terms of mean and standard deviation or median with interquartile range.

RESULTS
A total of sixteen patients were selected for the study. The average age of the study subjects was 47.75 ± 16.5 years. The age ranged between 16 to 73 years. There were 13 (81.25%) male and 3 (18.75%) female patients. There was history of occupational exposure among 8(50%) of the subjects in the form of handling cattle, milking them or drinking raw milk. Two patients were assistants to veterinarians. In 3 (18.75%) in-patient records occupation history was not documented. Eleven (68.75%) hailed from rural areas.

Considering the clinical features, all 16 (100%) subjects had presented with history of fever. The mean duration of fever was 21.25 days ± 20.08 days. It ranged from 7 days to 2.5 months.
Nine (56.25%) complained of fatigue, 4 (25%) of loss of appetite and 2 (12.5%) of weight loss. Ten (62.5%) of them had musculoskeletal symptoms in the form of myalgia or back pain. Four patients had severe spondylotic changes in the vertebrae, and one had a compression fracture. In one patient ANA was weakly positive without satisfying any other criteria for SLE.

Neurological manifestations such as altered sensorium, meningeal signs and/or hearing loss were present in 5 (31.25%) of them. Headache was a presenting symptom in 10 (62.5%) patients. Four (25%) patients complained of cough. Gastrointestinal symptoms were in the form of abdominal pain (n=8, 50%) and vomiting (n=5, 31.25%). Abdominal examination revealed hepatomegaly (n=2, 12.5%), splenomegaly (n=5, 31.25), hepatosplenomegaly (n=1, 6.25%) and in one (6.25%) patient even ascites. Clinical features are represented in Table 1.

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Frequency (n)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupational exposure</td>
<td>8</td>
<td>50</td>
</tr>
<tr>
<td>Occupation not known</td>
<td>3</td>
<td>18.75</td>
</tr>
<tr>
<td>Residence in rural areas</td>
<td>11</td>
<td>68.75</td>
</tr>
<tr>
<td>Symptoms and signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>16</td>
<td>100</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9</td>
<td>56.25</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>Weight loss</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body ache</td>
<td>10</td>
<td>62.5</td>
</tr>
<tr>
<td>Back ache</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered sensorium</td>
<td>3</td>
<td>18.75</td>
</tr>
<tr>
<td>Meningeal signs</td>
<td>3</td>
<td>18.75</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>3</td>
<td>18.75</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain abdomen</td>
<td>8</td>
<td>50</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5</td>
<td>31.25</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>5</td>
<td>31.25</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>1</td>
<td>6.25</td>
</tr>
<tr>
<td>Ascites</td>
<td>1</td>
<td>6.25</td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>1</td>
<td>6.25</td>
</tr>
<tr>
<td>Oedema</td>
<td>2</td>
<td>12.5</td>
</tr>
</tbody>
</table>

Table 1. Clinical Features

Considering patients presenting with organ specific involvement due to brucellosis, there were seven (43.75%) of them. Five (31.25%) were diagnosed with neurobrucellosis based on clinical presentation and cerebrospinal fluid analysis. Cerebrospinal fluid analysis in all 5 patients showed pleocytosis with total cells not exceeding 50 cells with lymphocytic predominance, and elevated protein. Glucose was low in 2 patients and normal in the rest. In 2 patients Brucella IgG was positive in CSF as well. One patient developed focal neurological deficit in the form of faciobrachial weakness which improved in 7 days with treatment.

Another patient had extensive spinal brucellosis and a brucellaoma in the liver. This was initially suspected to be a primary malignancy of the prostate (as the patient had an enlarged prostate) with metastasis to the liver and vertebral column.

Two (12.5%) patients presented with multiple organ involvement. One patient presented to the orthopedic surgeon with history of severe back pain, and was incidentally found to have ascites, treated by gastroenterologists before being referred to a physician for altered sensorium which occurred during the course of the illness. This patient was finally diagnosed to have meningoencephalitis with ascites secondary to brucellosis.

Blood investigations revealed anemia in 13 (81.25%) patients, mean hemoglobin in men being 11.62 ± 2.34 g/dL and in women 10.9 ± 1.32 g/dL. Many patients had normal leucocyte counts, with 2 (12.5%) having leukocytosis and 1 (6.25%) patient having leucopenia. Counts ranged from 3380 to 28580. Nine (56.25%) patients had thrombocytopenia. ESR was elevated in seven (43.75%) patients with mean ESR being 73.57 ± 36.6 mm/hr. There were eleven (68.75%) patients with an abnormal liver function test with transaminitis and an elevated alkaline phosphatase which averaged at 209.19 ± 121.2 IU/L. Chest X ray was abnormal in 5 (31.25%) patients with 3 patients having bronchopneumonia pattern and 2 having bilateral pleural effusion.

Brucella IgM was done in all patients with mean titre being 4.18 ± 3.46 IU/ml. Brucella IgG was done in only 3 patients and was positive in two.

Treatment protocols followed were different with doxycycline monotherapy in 4 (25%), doxycycline-rifampicin in 6 (37.5%), doxycycline-streptomycin in 4 (25%) and triple therapy (doxycycline-streptomycin-ceftiraxone) in 1 (6.25%) patient. In 1 (6.25%) patient where there was clinical suspicion of tuberculosis, both anti-tubercular therapy and doxycycline were given. This is depicted in Table 2.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency (n)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline + Rifampicin</td>
<td>6</td>
<td>37.5</td>
</tr>
<tr>
<td>Doxycycline + Streptomycin</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>Doxycycline + Streptomycin + Ceftriaxone</td>
<td>1</td>
<td>6.25</td>
</tr>
<tr>
<td>Doxycycline only</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>ATT + Doxycycline</td>
<td>1</td>
<td>6.25</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>16</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

Table 2. Treatment Protocols

Average duration of hospital stay was 19.13 ± 12.01 days and ranged between 6 to 49 days.

All our patients recovered from the illness, many of them showing improvement while in hospital. One patient expired in hospital due to co-infection with dengue haemorrhagic fever and ventilator associated pneumonia.
DISCUSSION
Brucellosis seems to be a much neglected disease in our country though it is stated to be the most common zoonosis worldwide. The true incidence in India is not known with only sporadic reports from some areas. The extrapolated incidence in India is 321 cases per year. Studies concentrating on the clinical aspects of the disease in our country are even fewer.

The patients in our study were mostly males like in other studies. The probable explanation for this is that men are more often involved in rearing cattle as compared to women who are more involved with household chores. The most common age of presentation seems to be in young adults like in our study who are mostly the workforce in any community. There was significant history of occupational exposure in half of our study subjects as in many other studies. And a significant proportion hailed from rural background where animal husbandry is a principal occupation besides agriculture.

All our patients presented with history of fever. Occurrence of fever in brucellosis is a universal phenomenon, however if left untreated for weeks the patient may become afebrile followed by a relapse. One patient in our study was admitted to hospital thrice over a span of three months with history of fever lasting for 10-15 days each time, before being diagnosed as having brucellosis. In all cases the initial differential diagnosis considered did not include brucellosis.

Other symptoms which were commonly reported from other studies were fatigue, myalgia, weight loss and gastrointestinal symptoms. These were seen among our patients as well. Musculoskeletal pain was a significantly disturbing symptom in many of our patients. These symptoms in brucellosis are fairly common with one author even stating that seropositivity for brucellosis is almost ten times higher for pyretic patients with backache than for those without backache. Autoimmune biomarkers may also be found in patients with this disease as we found in one of our patients.

The proportion of patients diagnosed with neurobrucellosis was considerably higher compared to other studies and may be due to the fact that ours is a higher centre where complicated cases get referred to. Cerebrospinal fluid typically depicted lymphocytic pleocytosis with elevated protein as in other studies. Three patients had hearing loss which is well documented in this disease, and should prompt a search for neurological involvement. Brucella organisms have a tropism for the auditory nerve.

Involvement of the reticuloendothelial system is common in brucellosis manifesting as hepatic, splenic and lymph node enlargement. Biochemical abnormalities most often noted are transaminitis and elevated alkaline phosphatase. Our study also reflected similar findings.

We had one patient presenting with an unusual liver mass namely hepatic brucelloma. This is a focal suppurative lesion in the liver associated with central or peripheral calcification. They appear as isoechoic or hypoechoic lesions.
on imaging. Similar lesions may be found in the spleen. They represent a complication of untreated brucellosis. In our patient the liver mass was associated with changes in the vertebral bodies which made the treating physician suspect malignancy with metastasis, and prompted a search for the primary tumour. Images 1, 2 and 3 depict the above findings.

Another patient, a cowherd by occupation presented to an orthopaedic surgeon with severe low back pain. He was found to have ascites. On analysis it turned out to be a low SAAG, high protein ascites and was being managed by gastroenterologists, before the patient developed altered sensorium and a physician was called in, who considered the possibility of brucellosis keeping in mind the occupational background of the patient. Ascites occurring in brucellosis is very rare and represents the response of the peritoneal mononuclear phagocytic system to the disease. These two cases highlight the fact that brucellosis is a deceptive disease.

Haematological abnormalities like high ESR, anaemia, thrombocytopenia and pancytopenia are reported from other studies as well. High ESR may predict a higher chance of complications occurring. A few patients had pulmonary manifestations presenting with fever and cough with chest x ray showing bronchopneumonia or an effusion pattern. These findings are reported in literature.

Enzyme immunoassay was used to diagnose brucellosis in our patients as this is the only available test in our centre. There are better diagnostic procedures such as PCR but they are more expensive. Twelve out of sixteen patients received optimal treatment while four patients received doxycycline monotherapy which is reported to be associated with higher disease relapse rates according to various studies. The authors of this study further suggest that there should be a common global language for the treatment of this disease.

We are likely to continue seeing cases of human brucellosis in our country. Hence, it is our assumption that there might be many such cases which remain undiagnosed in the community.

CONCLUSION
According to us this is one of the few studies which have dealt comprehensively with the protean manifestations of the disease. This is a diagnosis which is not often considered by doctors while treating patients particularly those who come with various combinations of system involvement. The importance of paying heed to the occupational background while diagnosing this disease cannot be over-stressed.

We saw such unusual presentations in the small number of patients studied even when clinical suspicion wasn’t high enough. It is our assumption that there might be many such cases which remain undiagnosed in the community.

With this study we conclude that all patients who are at risk need to be screened for the disease when they present with PUO or with unusual clinical manifestations. Efforts should be made in endemic areas to develop newer and better diagnostic facilities. And doctors should be aware of correct treatment protocols.

REFERENCES


