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Overview of Human Brucellosis in Aseer region, Saudi Arabia

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RESEARCH

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ABSTRACT

Background

Brucellosis is a common zoonotic disease of the Middle Eastern countries. Acute cases of brucellosis are often treated as cases of Pyrexia of unknown origin.

Aims

The main aim of this study is to compare the epidemiological, clinical and laboratory findings of the 42 culture positive cases of Brucella.

Methods

Forty two culture positive cases of Brucella were obtained from both in -patients and outpatients with a history of pyrexia over a period of two years (Nov 2014-Nov 2016). The patients' files were examined retrospectively for the history, clinical features, and lab findings.

Results

The prevalence of brucellosis was calculated to be 11.1 per cent as 42 cases were positive for brucellosis out of 377 of PUO cases Of the 42 cultures positive patients the percentage of males (57.1 per cent) were almost equal to the females(42.8 per cent). The mean±S.D age was 28.5±13.65. 28.5 per cent had a history of livestock associations (Chi-square 3.8889, a p-value of 0.048607) which was statistically significant. 26.2 per cent had a history of raw milk and dairy produce intake (Chi-Square 2.6276, p-value of 0.105023) this was not statistically significant. 9.5 per cent had a family history of brucellosis; this association was not statistically significant as well (chi-square statistic 1.8651, p-value of 0.172034). 61.9 per cent presented as acute cases, 30.9 per cent of sub-acute cases and 7.1 per cent as chronic cases respectively. The pre-dominant clinical symptom was Fever (100 per cent) with the commonest clinical signs being the osteoarticular signs (30.9 per cent). Raised ESR and CRP positives were seen in 34 cases (80.9 per cent) and 23 cases (55 per cent) respectively followed by Anaemia in 22 cases (52.3 per cent).

Forty two cases were blood culture positive. All the cases were sensitive to the recommended regimen of Doxycycline and streptomycin.

Conclusion

Brucellosis is still a major health problem in the Middle Eastern countries especially in the Kingdom of Saudi Arabia. Although latest diagnostic equipment are available lacunae in the skill and knowledge prove to be a disadvantage. This scenario may lead to blind treatment which in turn can lead to the development of antibiotic resistance which is another problem altogether.

Key Words

Brucellosis, Middle Eastern countries, pyrexia of unknown origin, blood culture positive cases, clinical findings

What this study adds:

1. What is known about this subject?

Brucellosis continues to pose a serious threat to the Public health even in these recent times especially in the Middle East and is considered important among the zoonotic infections prevalent worldwide.

2. What new information is offered in this study?
Osteoarticular brucellosis was the common form of brucellosis found in these parts of Saudi Arabia.

3. What are the implications for research, policy, or practice?
Although previous studies have indicated the need for a National Brucellosis control program in Saudi Arabia, there is one yet to be established. In order to control Animal brucellosis and thereby prevent Human brucellosis, there is a need for the practice of correct animal husbandry. Early diagnosis and treatment will bring down the burden of the disease.

Background

Brucella a small gram-negative coccobacillus has become famous in the last 100 years. The common species of Brucella which are pathogenic to man are *B. melitensis*, *B. abortus B. canis*, and *B. suis*.[1] Brucellosis is normally acquired by humans when in contact with infected/contaminated animals and can be called a zoonotic disease. It is also an occupational disease as it affects Farmers, butchers, and veterinarians.[2,3] It is acquired by the consumption of unpasteurized milk especially the camel's milk, a common practice found in the Middle Eastern countries.[4] It is a major health problem in the Middle East, parts of Asia, Africa, and South America.[5] The common clinical presentation of Brucellosis in man is Pyrexia of Unknown origin.[6,7] The disease is known to affect other various organs and have a varied presentation. The main aim of the present study is to compare and dwell on the clinical, laboratory findings of blood culture positive cases of brucellosis detected over a period of 2 years in a tertiary care hospital in the Aseer province of the Kingdom of Saudi Arabia. In this province, acute brucellosis is often treated as Pyrexia of unknown origin without proper confirmation with a variety of antibiotics which in the course of time can lead to resistant cases of Brucellosis. A precise identification with antibiotic susceptibility testing would prevent this scenario.

Method

Sample Frame

A total of 42 culture positive cases of Brucella were obtained from various specimens like Blood, CSF and synovial fluid collected over a period of 2 years (November 2014- November 2016) from patients who had presented with a history of fever for more than a week

Recruitment methods

All the patients with a history of pyrexia who had attended the hospital over this time period (Nov 2014-Nov 2016) were included in the study.

Case definition

The case definition of Brucellosis as per CDC is as follows *"An illness characterized by acute or insidious onset of fever and one or more of the following: night sweats, arthralgia, headache, fatigue, anorexia, myalgia, weight loss, arthritis/spondylitis, meningitis, or focal organ involvement (endocarditis, orchitis/epididymitis, hepatomegaly, splenomegaly)"*.[8]

The common clinical presentations of acute brucellosis are fever, chills, fatigue sweating and weight loss. Sub-Acute clinical presentations are much milder than acute cases. Chronic Brucellosis present with complaints of malaise, depression, nervousness generalized body ache and musculoskeletal pain.[9]

Data collection: This is a retrospective study. The patient's files were investigated for the history and the clinical findings

Analysis: The isolates were identified by the colony morphology, Gram stain, oxidase, catalase and by Vitek II compact (bioMerieux, Durham USA). Positive cultures were identified and confirmed by automated culture id system BACTEC FX (Becton Dickinson USA).

Antibiotic susceptibility testing: The antibiotic susceptibility of five antibiotics like Doxycycline, Tetracycline, Gentamicin, Streptomycin, Trimethoprim/sulfamethoxazole was done by using a gradient strip method (E-test strips bioMerieux, Marcy L'Etoile, France). The E strips were placed on the Muller Hinton agar and read after 48 hours incubation at 37-degree centigrade. The MIC was calculated as the value at which the zone of inhibition intercepted the E -test strip scale and the range of MIC values was calculated. For Quality control, the reference strains like *E. coli* ATCC 25922, *S. pneumoniae* ATCC 49619 and *S. aureus* ATCC 29213 were used.

Results

All the 42 isolates were identified by Vitek II as *B. melitensis*. Of the 42 isolates, 37 were isolated from the blood, 4 from the joint and 1 from the CSF. Of the 42 culture positive cases The MIC range for each antibiotic was as follows Doxycycline 0.023–0.5mg/L, Tetracycline 0.032–0.75mg/L, Gentamicin 0.047–2mg/L, Streptomycin 0.125–2mg/L and Trimethoprim/Sulfamethoxazole 0.016–1mg/L.

All the 42 isolates were sensitive to Doxycycline, Tetracycline Gentamicin, Streptomycin and Trimethoprim/sulfamethoxazole.

Of the 42 culture, positive patients 18 (42.8 per cent) were female and 24 (57.1 per cent) were males. The mean±SD age of the 42 patients was 28.50±13.65. Figure 1 summarizes the age distribution.

One (2.3 per cent) belonged to the age group between 1–10 years, 12(28.5 per cent) to the age group 11–20 years, 13(30.9 per cent) to the age group 21–30, 8(19 per cent) to the age group 31–40, 5 (11.9 per cent) to the age group 41–50, 2(4.6 per cent) to the age group 51–60 and 1(2.3 per cent) belonged to the age group of 61–70.

There was a history of association with livestock in about 12 cases (28.5 per cent). There is no history of any occupational risk for brucellosis in the rest of the 30 cases.

The chi-square was calculated to see if the association with livestock and Clinical Brucellosis was significant. The chi-square statistic was 3.8889 with the p-value of 0.048607, thus indicating the association with the livestock was significant with $p<0.05$. There was a family history of brucellosis in about 4 cases (9.5 per cent). On chi-square analysis, the chi-square statistic was 1.8651 with a p-value of 0.172034 and the result was not significant at $p<0.05$. There was a history of raw milk and dairy products consumption in 11 cases (26.2 per cent). The chi-square was 2.6276 with a p-value of 0.105023 and the result was not significant at $p<0.05$. The details are clearly illustrated in the Tables 1-3 and Figure 2.

Clinically the 42 cases were divided into acute cases 26, sub-acute cases 13 and chronic cases 3. The data is illustrated in Figure 3.

The clinical symptoms among the 42 isolates are depicted in Table 4, the lab findings in Table 5 and the specific lab findings in Table 6 respectively.

Discussion

According to WHO Brucellosis is a zoonotic non-malarial febrile illness categorized under the neglected zoonotic disease. The prevention and decrease of the occurrence of the disease in humans requires elimination of the zoonotic disease in their respective animal reservoirs.[10]

The people of Saudi Arabia by tradition consume raw camel's milk and have close contact with the animals especially camels.[11] In the previous years, Brucella was detected in Saudi Arabia by Culture and Serology.[12] Important advances have been made to diagnose Brucellosis by automated blood culture techniques. However, in many places, people still rely on serological tests and ELISA.[13] In our study, the Brucella cultures were identified by BACTEC FX (Becton Dickinson USA) from samples like blood, CSF, and joint fluid. This was further identified and confirmed by Vitek II as *B. melitensis*.

The actual rates of Brucellosis in endemic countries especially the Middle East countries are much higher and are under reported due to the poor diagnostic measures.[14] The situation is the same in Saudi Arabia as most of the time the plates are discarded without waiting for the required period of time thus exhibiting the lack of knowledge. The prevalence of Brucellosis in Saudi Arabia was found to be 15 per cent.[15] In another study done in the Jizan province of Saudi, the prevalence was found to be 13.4 percent.[16] In our study out of 377 cases of Pyrexia of unknown origin admitted over a period of 2 years 42 positive cases were identified as *B. melitensis* and the prevalence was 11.1 per cent. This prevalence is almost the same as the other rates reported in Saudi Arabia.

Brucellosis is common in the age group of 15–35 years in most of the endemic countries.[17] In our study of the 42 culture, positive patients 73.8 per cent (31) belonged to the age group between 15-35 years. The mean age was 28.50±13.65 with 42.8 per cent females and 57.1 per cent males. The reason for the high percentage of females with brucellosis could be that most of these females belonged to the rural population and thus had equal responsibility in taking care of the livestock as the men. However, the percentage of females is almost the same as that of the percentage of males with brucellosis as in correlation with studies done in Saudi Arabia where there was not much of a difference in the prevalence of brucellosis among the females and the males.[18]

The main route of transmission of Brucellosis is by the consumption of raw unpasteurized dairy products. This is common, especially in the endemic countries. In most of the developed nations brucellosis is acquired by the occupational exposure especially in occupations like veterinary medicine, farming, and butchery. It can be acquired in accidental laboratory exposures as well.[17] In our study, there is a history of consumption of raw milk and dairy products in 26.2 per cent of the culture-positive patients. However, by Chi-square analysis, this association was not significant at $p<0.05$. In another similar study

conducted in Saudi Arabia, the percentage of the people who consumed raw milk was 7.5 per cent (Odds ratio=4.4) and dairy products 5.9 per cent (Odds ratio=2.4 thus indicating a strong association of brucellosis with the consumption of raw milk and unpasteurized dairy products. In the same study from Saudi Arabia, the percentage of people who had a close association with livestock was around 14.2 per cent whereas in our study the percentage of culture positive patients who had a close association with animals and livestock was found to be 28.5 per cent.[18] From the chi-square analysis this association was found to be significant with a p- value of 0.04 which indicates that the result is significant with $p<0.05$. Brucellosis can present as acute, sub-acute and chronic. In our study of the 42 positive cases, 61.9 per cent had an acute presentation, 30.9 per cent had a sub-acute presentation 6.9 per cent presented as chronic cases.

Many studies have been done which prove that screening of family members of patients with acute brucellosis can help in the detection of new cases.[19] However, in our study by chi-square analysis, the association between brucellosis and any family history of brucellosis was found to be not significant with the $p<0.05$. This could be probably because of the low number of cases with the family history of brucellosis.

Other than close contact with livestock, consumption of unpasteurized milk as the causative factors of brucellosis frequent travel to endemic areas should also be considered as the causative factor of Brucellosis. Globalization has made travel frequent, fast and easy thus people who frequently travel to endemic areas like Asia, Africa, Mediterranean basin and the middle east are at a higher risk of acquiring the infection.[20] Brucellosis is the major cause of Pyrexia of unknown origin so if one encounters such patients in non-endemic areas and if the patient is also a frequent traveller then one must keep the diagnosis of Brucellosis in the forefront.

In our study the common clinical presentations were fever (100 per cent) followed by fatigue (80.9 per cent), arthralgia (71.4 per cent), sweating (69 per cent), lack of appetite (45.2 per cent) and weight loss (42.8 per cent). Other symptoms include Nausea/vomiting (19 per cent) a headache (16.6 per cent) and stiff neck/altered sensorium (2.4 per cent). Organomegaly is a common sign in Brucellosis. The liver is commonly affected and enlarged with elevated liver enzymes.[17] In our study hepatomegaly (23.8 per cent) was seen in most of the positive cases with increased ALT/AST levels (24 per cent).

Splenomegaly (16.6 per cent), Hepatosplenomegaly (16.6 per cent) and Lymphadenopathy (16.9 per cent) were the other clinical signs seen in our study. Osteoarticular brucellosis is a common form of focal brucellosis. In our study about 30.9 per cent of the cases had osteoarticular involvement, not differing from a study from Macedonia where the percentage was 43.9 percent.[21] Studies were done in Saudi Arabia as early as 1990 have reported a prevalence of 38 per cent for osteoarticular complications with consumption of raw milk and contact with infected animals as the main causative factor. This prevalence was similar to the adults but with a difference in the bone and joint involvement.[22]

Recently a rare case of olecranon bursitis with negative serology, positive blood cultures, and aspirate cultures was reported from Riyadh Saudi Arabia. In our study, although osteoarticular involvement was the highest none of the cases had isolated involvement of the bursa.[23]

Literature from Saudi Arabia has shown that 47.7 per cent of the clinically diagnosed brucellosis patients had osteoarticular involvement with sacroiliitis, peripheral arthritis and destructive spondylitis as common presentations.[24]

Osteoarticular brucellosis is also common in non-endemic areas. A study done in North-western Spain reported that 27.8 per cent of the 44 brucellosis patients had osteoarticular complications. Although this is not high as compared to the endemic area, osteoarticular involvement was fairly a common presentation.[25]

The abnormal laboratory findings were anaemia, Lymphocytosis, Pancytopenia and elevated levels of ESR, ALT/AST, and CRP levels. The laboratory findings were in correlation with the clinical findings. All the 42 cases were culture positive. 88 per cent were isolated from the blood 9.5 per cent from the joints and 2.4 per cent from the C.S.F. Isolation from the blood or the bone marrow indicates a definite diagnosis. The one case which was isolated from the C.S.F did have neurological manifestations of the disease. In other studies, the CNS involvement was found to be around 1.3–2 per cent.[26]

In our study, all the positive cases of Brucellosis were treated with varied antibiotic regimens. A combination of Doxycycline, Rifampicin, and ceftriaxone was effective in the treatment of Neurobrucellosis. A combination of the same or different combination like Doxycycline plus rifampicin was used for other clinical presentations as there is no

standard antibiotic therapy protocol for Brucellosis.

Conclusion

Our study gives a varied and detailed clinical picture of Brucellosis, the prevalence of the disease among the PUO cases and a detailed laboratory picture. All the 42 cases were positive for *B. melitensis* in accordance to the epidemiological picture presented in Saudi Arabia. A close association of both the men and women between the age groups 15-35 years with the livestock indicates that close contact with animals could be a causative factor of the disease. Brucellosis in Saudi Arabia is common and has high morbidity and economic loss due to the disease. Due to lack of technique and knowledge of the disease and improper diagnostic protocols of clinicians and indiscriminate usage of antibiotics, many a time the disease is not identified and the cases are treated blindly as PUO without proper identification.

We can get away with this as the organism is still responsive to antibiotics. What happens when it becomes resistant? This is something which should be reflected upon seriously by the Clinicians in Saudi Arabia. Preventive control measures should be implemented in Saudi Arabia to control the disease which still can pose a threat in Modern times equipped with all the advantages of latest diagnostic techniques.

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PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

FUNDING

None

ETHICS COMMITTEE APPROVAL

Since this is a retrospective study and a lab-based study the ethical approval was not necessary.

Figures and Tables

Figure 1: Age Distribution

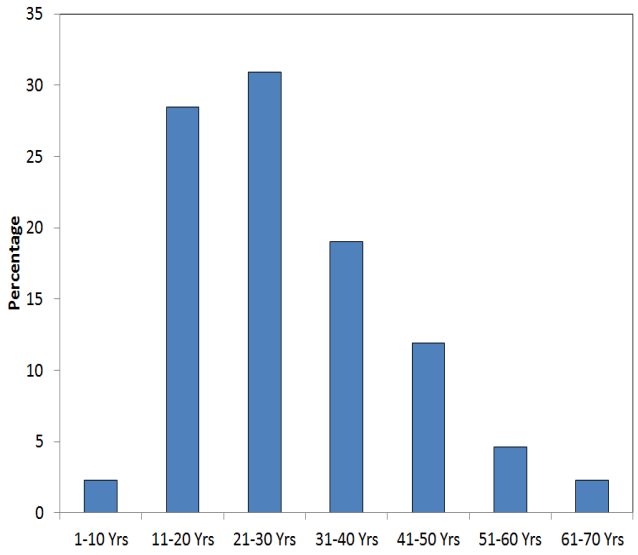

Figure 2: Bar graph depicting the distribution of livestock association, family history, and raw dairy products consumption

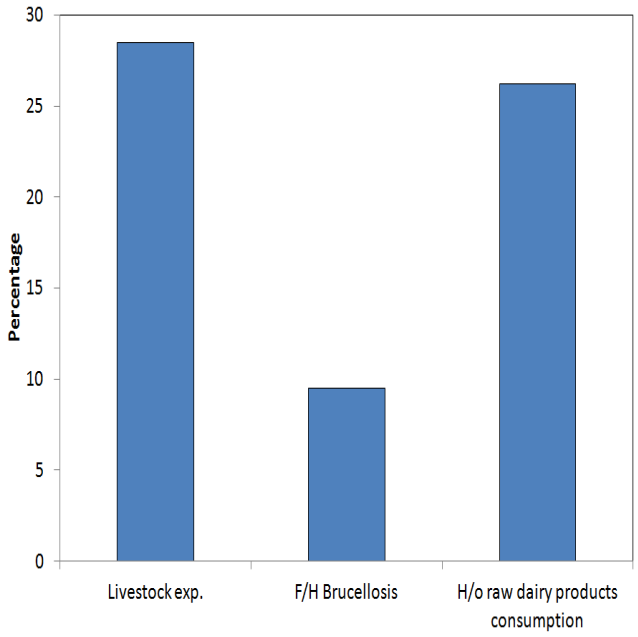

Figure 3: Pie chart depicting the clinical distribution of the cases

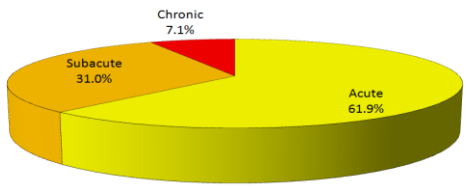

Table 1: Chi Square analysis

Gender	Associated with Livestock			Not Associated with Livestock			
	Observed Total	Expected total	Chi-square	Observed total	Expected Total	Chi-square	Row total
Male	8	5.14	1.59	10	12.86	0.63	18
Female	4	6.86	1.19	20	17.14	0.48	24
Column total	12			30			42(Grand total)

The chi-square statistic is 3.8889. The p-value is 0.048607. This result is significant at $p<0.05$.

Table 2: Chi Square analysis

Gender	H/O Raw milk, dairy products consumption			No H/O Raw milk, dairy products consumption			
	Observed Total	Expected total	Chi-square	Observed total	Expected Total	Chi-square	Row total
Male	7	4.71	1.11	11	13.29	0.39	18
Female	4	6.29	0.83	20	17.71	0.29	24
Column total	11						42(Grand total)

The chi-square statistic is 2.6276. The p-value is 0.105023. This result is not significant at $p<0.05$.

Table 3: Chi-square analysis

Gender	Family history of Brucellosis			No Family history of Brucellosis			
	Observed Total	Expected total	Chi-square	Observed total	Expected Total	Chi-square	Row total
Male	3	1.71	0.96	15	16.29	0.1	18
Female	1	2.29	0.72	23	21.71	0.08	24
Column total	4						42(Grand total)

The chi-square statistic is 1.8651. The p-value is 0.172034. This result is not significant at $p<0.05$.

Table 4: Clinical symptoms and signs

Clinical symptoms	No of cases	Percentage
Fever	42	100%
Fatigue	34	80.9%
Sweating	29	69%
Arthralgia	30	71.4%
Lack of appetite	19	45.2%
Nausea/Vomiting	8	19%
Headache	7	16.6%
Backache	12	28.5%
Weight loss	18	42.8%
Signs		
Hepatomegaly	10	23.8%
Splenomegaly	7	16.6%
Hepatosplenomegaly	7	16.6%
Lymphadenopathy	3	16.9%
Stiff neck/ altered sensorium/CNS	1	2.4%
Osteoarticular	13	30.9%

Table 5: Lab findings total number 42

Lab parameters	n	%
Anaemia	22	52.3%
Leukopenia	7	16.6%
Thrombocytopenia	5	12%
Pancytopenia	2	4.7%
Lymphocytosis	12	28.5%
ESR>20	34	80.9%
ALT/AST Elevation	10	24%
CRP positive	23	55%

Table 6: Specific lab findings

Lab parameters	n	%
Culture Positive cases	42	100
Blood	37	88%
Joint	4	9.5%
CSF	1	2.4%