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Full Length Research Paper

Study of epidemiological features of Brucellosis in Kuwait

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The aim of this study was to report the epidemiologic, clinical features and imaging findings, for a series of brucellosis patients in Kuwait. Patients and methods: This is a retrospective analytic study, data obtained from medical records of brucellosis patients (between 1st January 2008 and 31st December 2012). The investigation involved 220 patients (182 males and 38 females, mean age 42 years, range 3-68), and identified 21 patients with vertebral involvement. In all patients demographic, clinical and laboratory workups data were recorded. In addition radiography, radionuclide bone scintigraphy and MRI had been for patients with spinal involvement. The disease was acute in 33.6%, subacute in 20% and chronic in 46.4% of the cases. Most of the patients aged between 15 and 45 years (73.7%), (82.7%) were male and only (17.3%) female. In 192 patients (87.3%), the source of infection was unpasteurized milk. Twenty-three (10.5%) of the infected individuals had direct contact with animals (sheep or cattle).Thirty-two (84.2%) of the 38 infected females worked at domestic duties at home. Twenty-five (11.4%) of the 220 patients were farmers, seven (3.2%) were laboratory personnel, and four (1.8%) were veterinarians. Twenty-nine patients (13.2%) had a family history of brucellosis. MRI revealed spondylodiskitis in 21 cases (9.5% of the 220 total). Human brucellosis is preventable and legislation should be enacted to strictly require pasteurization of milk and dairy products. Public health education aims to prevent the transmission of brucellosis from animals to humans. Also, serologic testing, quarantine, and other precautionary measures at frontiers to prevent importation of infected animals

Keyword: epidemiologic, clinical features, brucellosis patients, Kuwait

INTRODUCTION

Brucellosis is the most common zoonotic infection worldwide (Pappas et al., 2006). It is endemic in the Mediterranean region, the Middle East, Arabian Gulf, Latin America and parts of Asia and Africa, but the epidemiology is changing over the last decades due to socioeconomic changes, improved disease recognition and eradication programmes (Pappas et al., 2006).

Brucellosis was endemic in Kuwait, reported infection rates increased in the 1980s from 5.1 in 1982 to 68.9 per 100,000 population in 1985 (Adel Shehata1 et al., 2001). Since the beginning of the 1990s, it had decreased reaching the level 2.1 per 100,000 population in 2006 (Ministry of Health, 2006).

Brucellosis is primarily a contagious disease of domestic animals: goats, sheep, cows, camels and dogs. Inter-human transmission of brucellosis has been rarely reported. Humans are commonly infected through ingestion of raw milk, cheese or meat, or through direct contact with infected animals, products of conception or animal discharges (e.g., among shepherds, farmers and veterinarians), and through inhalation of infectious aerosols (e.g., by workers in abattoirs and microbiology laboratories) (Al-Eissa, 1990; Al-Eissa et al., 1992).

This bacterium has a unique ability of invading both phagocytic and non-phagocytic cells and surviving in the intracellular environment by avoiding the immune system in different ways. This is why brucellosis is a systemic disease and can involve almost every organ system. When involvement of a specific organ predominates, the disease referred to as focal or localized (Gonzalez-Gay et al., 1999).

Among the species known to cause disease in

humans, *B melitensis* is thought to be the most virulent and causes the most severe and acute cases of brucellosis. This species is also the most prevalent worldwide. A prolonged course of illness, often associated with suppurative destructive lesions is associated with *B suis* infections. *B abortus* is associated with mild-to-moderate sporadic disease that is rarely associated with complications; the case-fatality rate of untreated brucellosis is 2% or less and usually results from endocarditis caused by *B melitensis* infections (Young, 2000).

Incubation period can vary from 1-6 weeks or many months. Symptoms of brucellosis are protein in nature, and none is specific enough to support the diagnosis. These symptoms include fever, sweating, constitutional symptoms (as anorexia, asthenia, fatigue, malaise and headache) bone and joint symptoms, also neuro-psychiatric, gastrointestinal and respiratory symptoms (Young, 1995).

Physical findings in patients with brucellosis are variable and non specific for the disease, the most common findings are hepato-splenomegaly (or isolated hepatomegaly or splenomegaly), lymphadenopathy and osteoarticular involvement (Al-Eissa, 1993). Occasionally symptoms related to a single organ predominate, in which case the disease is termed localized. Skeletal, gastrointestinal and hematologic complications are the most common (Al-Eissa et al., 1993), but involvement of the heart and nervous system is the most serious (Al-Eissa, 1995). Hepatitis probably occurs in most infected patients during the course of their illness, and liver function tests commonly demonstrate hepatic involvement (Al-Aska, 1989).

Brucellosis was diagnosed by serological analysis (Brucella agglutinin titer≥ 1/160) or by clinical symptoms combined with a positive blood culture. Clinically, identification to the genus level is adequate to initiate therapy, and the type of species involved does not alter the therapeutic agents used. Some general laboratory findings might suggest the diagnosis (eg, leucopenia, relative lymphocytosis, and pancytopenia). Slight elevation in liver enzymes is a very common finding (Young, 1991).

Osteoarticular involvement (peripheral arthritis, sacroiliitis, spondylitis, osteomyelitis, and bursitis) is the most frequent complication of brucellosis (20%-60% of cases), in which the diagnosis of brucellar spondylodiscitis is often difficult since the clinical presentation may be obscured by many other conditions and because of the long latent period (Young, 1995. The axial skeleton is the most common site of involvement with a frequency ranging from 2% to 53%. Multiple-level spinal involvements are rare (Rajapakse et al., 1987).

Radiographs of the spine, bone scan, and Computed Tomography (CT) scan provide insufficient data and Magnetic Resonance Imaging (MRI) is the investigation method of choice in diagnosing brucellar spondylodiscitis (Colmenero et al., 1991). Advantages of MR imaging include the capability of multiplanar imaging, direct evaluation of the bone marrow, and simultaneous visualization of the neural structures (Khateeb et al., 1990; Benjamin and Khan, 1994). Though it is not always possible to differentiate various infections on the basis of imaging findings alone, there are certain features which along with a good clinical background can differentiate brucellar spondylitis from other spinal infections. It is useful to follow up such patients after specific treatment to further confirm the diagnosis (Tasova et al., 1999; Geyik et al., 2002).

The aim of this study was to report the epidemiologic, clinical features and imaging findings, for a series of brucellosis patients in Kuwait

METHODOLOGY

Patients and Methods

This is a retrospective analytic study carried out in Kuwait Sabah Medical Area Hospitals. Data obtained from medical records of patients discharged with a diagnosis of brucellosis (between 1st January 2008 and 31st December 2012. The investigation involved 220 patients with brucellosis (182 males and 38 females, mean age 42 years, range 3-68), and identified 21 patients with vertebral involvement.

Diagnosis of brucellosis was done on the basis of the clinical presentation compatible with brucellosis such as: continued, intermittent or irregular fever of variable duration, headache, weakness, profuse sweating, chills, arthralgia, depression, weight loss, generalized aching, hepatomegaly and splenomegaly, confirmed by the detection of specific antibodies at significant titers and/or demonstration of an at least fourfold rise in antibody titer in serum specimens obtained 3 to 4 weeks apart. Significant titers were determined to be Standard Tube Agglutination Test (SAT) ≥1/160 and anti brucella Coombs test ≥ 1/320 (Young, 1991).

In all patients demographic, clinical and laboratory workups data were recorded. The following laboratory parameters were examined: Complete Blood Count (CBC), Erythrocyte Sedimentation Rate (ESR), Liver Enzymes (ALT and AST), C - reactive protein (CRP), Rheumatoid Factor (RF), and Antistreptolizin-O Titer (AST-O).

Based on the systemic disease duration before hospital admission, patients were classified as having acute brucellosis (<3 months), subacute brucellosis (3–12 months), or chronic brucellosis (>12 months) (Gotuzzo et al., 1982).

Spondylitis was defined as inflammatory back pain and stiffness along with radiological and/or CT changes of the spine and/or positive radionuclide bone scan with Tc-99m. Coxitis was confirmed by radiography and/or radionuclide bone scan with Tc-99m, and/or ultrasound

Table 1: Age and sex distribution of the 220 brucellosis patients

Age (years)	Males		Females		Total	
	No.	%	No.	%	No	%
≤15	26	11.8	8	3.6	34	15.5
15- <25	58	26.4	13	5.9	71	32.3
25- <35	46	20.9	12	5.5	58	26.4
35- <45	31	14.1	2	0.9	33	15.0
45- <55	14	6.4	3	1.4	17	7.7
≥55	7	3.2	-	-	7	3.2
Total	182	82.7	38	17.3	220	100

Table 2: Distribution of the 220 brucellosis patients by nationalities and hospitalization period

Nationality	Patients		Mean hospitalization period	
	No.	%	Males	Females
Bangladeshis	95	43.2	8	-
Indians	41	18.6	4	6
Kuwaitis	39	17.7	7	9
Non-Kuwaitis	22	10	4	8
Egyptians	13	5.9	3	5
Others	10	4.5	4	7
Total	220	100	5	7

examination. All the patients with spinal involvement were tested for tuberculosis. In addition, radiography, radionuclide bone scintigraphy and MRI were performed in all patients with clinical signs that suggested spondylodiskitis (Mile Bosilkovskiet al., 2004). MRI was performed using a 1.5-T magnet (Vision, Siemens Medical Solutions) with a spine coil. The following spinal MR sequences were obtained: axial and sagittal spin-echo T1-weighted images (TR/TE, 520/14), axial and sagittal turbo spin-echo T2-weighted images (4,000/99), sagittal fat-suppressed T2-weighted images, and contrast-enhanced axial and sagittal spin-echo T1-weighted images (0.1 mml/kg of gadopentetate dimeglumine [Magnevist, Schering] administered IV). The MRI parameters were as follows: field of view, 20-25 cm for the axial plane and 30-35 cm for the sagittal plane; number of excitations, matrix size, 256 x 132; slice thickness, 4 mm; intersection gap, 1 mm; and echo-train length (Aysin et al., 2006).

Statistical Analysis

The patient's age, illness and arthritis duration and follow-up period were presented using median and range values. Chi-squared test with Yates' correction and Fisher exact test were used for qualitative variables. For quantitative variables the comparison was performed using f-test. P values <0.05 were considered significant. Statistical analysis was preformed using SPSS statistical package for Windows, version 12.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Table 1, over a 5-years period, 220 cases of brucellosis were identified. Of these, 182 (82.7%) cases were male and 38 (17.3%) female, giving a male: female ratio of 4.8:1.0. Ages ranged from 3-68 years. Most of the 220 brucellosis patients were young and middle-aged adults; relatively few were children or elderly individuals.

In Table 2, the disease was more prevalent among Bangladeshis (43.2%), if we exclude the Bangladeshi patients (95 cases and all males), the male to female ratio would be 2.3:1. The mean hospitalization period was five days for males and seven for females. The mean hospitalization period was longest (8 days) for Bangladeshis and Kuwaitis and shortest for Egyptians (4 days).

In 192 patients (87.3%), the source of infection was

Table 3: Number and percent distribution of the 220 brucellosis patients by mode of transmission, occupation and family history

Mode of transmission	Unpasteurized milk	192 (87.3%)
	Direct contact with animals	23 (10.5%)
	Domestic duties at home in females	32 (84.2%)
Occupation	Farmers	25 (11.4%)
	Laboratory personnel	7 (3.2%)
	Veterinarians	4 (1.8%)
Family history		29(13.2%)

Table 4: Clinical manifestations of 220 patients at different stages of brucellosis

Symptoms and signs	Stage						Total		P-Value
	Acute (n = 74)		Subacute (n = 44)		Chronic (n = 102)				
	No.	%	No.	%	No.	%	No.	%	
Symptoms:									
Arthralgia	45	20.5	35	15.9	94	***42.7***	174	79.1	< 0.05
Fatigue	72	***32.7***	36	16.4	60	27.3	168	76.4	< 0.05
Back pain	54	24.5	28	12.7	60	27.3	142	64.5	> 0.05
Fever	68	***30.9***	28	12.7	42	19.1	138	62.7	< 0.05
Sweating	52	***23.6***	23	10.5	47	21.4	122	55.5	< 0.05
Headache	46	***20.9***	25	11.4	43	19.5	114	51.8	< 0.05
Palpitations	16	7.3	30	***13.6***	21	9.5	67	30.5	< 0.05
Appetite loss	22	10	14	6.4	19	8.6	55	25	> 0.05
Nausea	24	10.9	11	5	18	8.2	53	24.1	> 0.05
Abdominal pain	19	8.6	12	5.5	17	7.7	48	21.8	> 0.05
Anxiety	16	7.3	8	3.6	20	9.1	44	20	> 0.05
Weight loss	13	5.9	18	***8.2***	7	3.2	38	17.3	< 0.05
Cutaneous lesions	10	4.5	9	4.1	15	6.8	34	15.5	> 0.05
Chest pain	9	4.1	6	2.7	13	5.9	28	12.7	> 0.05
Diarrhea	11	***5***	8	3.6	4	1.8	23	10.5	< 0.05
Depression	9	4.1	2	0.9	7	3.2	18	8.2	> 0.05
Cough	5	2.3	3	1.4	8	3.6	16	7.3	> 0.05
Scrotal pain and swellings	4	-	-	-	-	-	4 (3.1% of	-	-
Signs:									
Hepatomegally	5	2.3	3	1.4	10	4.5	18	8.2	> 0.05
Splenomegaly	21	***9.5***	8	3.6	6	2.7	35	15.9	< 0.05
Hepatosplenomegaly	24	10.9	33	***15***	9	4.1	66	30	< 0.05
Lymphadenopathy	42	***19.1***	28	12.7	10	4.5	80	36.4	< 0.05

Note: Percentages are of all 220 patients except in scrotal pain and swellings.

unpasteurized milk and milk products, most commonly cheese. Twenty-three (10.5%) of the infected individuals had direct contact with animals (sheep or cattle).Thirty-two (84.2%) of the 38 infected females worked in domestic duties at home. Twenty-five (11.4%) of the 220 patients were farmers, seven (3.2%) were laboratory personnel, and four (1.8%) were veterinarians. Twenty-nine patients (13.2%) had a family history of brucellosis (table 3).

In table 4. Brucella was acute in 74 (33.6%), subacute

Table (5): Hematologic and biochemical findings in 220 patients at different stages of disease

Laboratory finding	Stage						Total		P-Value
	Acute (n = 74)		Subacute (n = 44)		Chronic (n = 102)				
	No.	%	No.	%	No.	%	No.	%	
Elevated Erythrocyte Sedimentation Rate (ESR)	50	22.7	29	13.2	36	16.4	115	52.3	< 0.05
Anemia	28	12.7	14	6.4	23	10.5	65	29.5	> 0.05
Elevated serum C-reactive protein (CRP)	30	13.6	9	4.1	13	5.9	52	23.6	< 0.05
Elevated transaminases	11	5	5	2.3	2	0.9	18	8.2	< 0.05

Note: Percentages are of all 220 patients

Table (6): Distribution of 21 patients with brucellar spondylodiskitis by: demographic characteristics, spinal level affection, disease stage and laboratory findings

Variable	No.	%	P-Value
Age (year):	52.2 ± 9.6	-	-
Sex:			
• Male	14	66.67	
• female	7	33.33	< 0.05
Spinal Level :			
• Lumbar	7	33.33	
• Thoracolumbar	4	19.04	
• Lumbosacral	2	09.52	< 0.05
• Thoracic	5	23.83	
• Cervical	3	14.28	
Disease stage:			
• Acute	11	52.38	
• Sub acute	6	28.57	< 0.05
• Chronic	4	19.05	
Bone abscess:	5	23.80	-
Blood culture	9	42.85	< 0.05
Agglutination titer:			
• 1/160	7	33.33	
• 1/320	6	28.57	> 0.05
• 1/640	5	23.82	
• 1/1280	3	14.28	

in 44 (20%), and chronic in 102 (46.4%) of the cases. The frequencies of fatigue, fever, sweating, headache, diarrhea, splenomegaly and Lymphadenopathy were significantly higher in the acute stage than in the subacute or chronic stages ($p<0.05$). Palpitations, weight loss and hepatosplenomegaly were significantly more frequent in the subacute stage than in the acute and chronic stages ($p<0.05$), and osteoarticular manifestations were significantly more frequent in the chronic stage than in the acute and subacute stages ($p<0.05$). No significant differences were seen among the three disease-stage groups with respect to rates of back pain, appetite loss, nausea, abdominal pain, anxiety, cutaneous lesion, chest pain, depression, cough or hepatomegally ($p>0.05$).

Blood testing revealed elevated ESR in 115 patients (52.3%), anemia (hemoglobin < 13 g/dL in males, hemoglobin < 12 g/dL in females) in 65 (29.5%), elevated CRP in 52 (23.6%), and elevated transaminases levels in 18 (8.2%). The frequencies of *elevated ESR, elevated CRP and elevated transaminases* were significantly higher in the acute stage than in the subacute or chronic stages ($p<0.05$). Statistical analysis revealed *no significant differences* among the three groups with respect to frequencies of anemia ($p>0.05$) Table 5.

In table 6, MRI revealed spondylodiskitis in 21 cases (9.5% of the 220 total), two third were male (66.7). The frequency of lumbar spondylodiskitis was significantly higher than the frequencies of thoracic and cervical

spondylodiskitis ($p < 0.05$ for both).

Eleven (52.4%) of these patients had acute brucellosis, six (28.6%) were in the subacute stage and four (19.1%) were in the chronic stage. Bone abscess developed in (23.8%) of the patients and blood cultures were positive in (42.9%) of them. No significant difference was found regarding brucella agglutination titer.

DISCUSSION

The epidemiology of brucellosis in Kuwait was changed over the last decades, reported infection rates decreased from 68.9 per 100,000 population in 1985 (Adel Shehata1 et al., 2001) reaching the level 2.1 per 100,000 population in 2006 (Ministry of Health, 2006). This is may be attributed to socio-economic changes, improved disease recognition and eradication programmes among animals.

Brucellosis can occur at any age but the most common age groups involved are adolescents and young adults (Chomel et al., 1994). In this study the disease mainly affected the most productive group in the community, because most of the patients with or without musculoskeletal involvement were aged between 15 and 45 years (73.7%). These results clearly show how the age range reflects the magnitude of the socio-economic and cultural impact of brucellosis.

According to published studies, both sex are affected equally (Ta¸sova et al., 1999; Malik, 1997), though brucellosis had long been recognized as an occupational disease primarily affecting adult males (Taylor and Perdue, 1988). In our study: (82.7%) of cases were male and only (17.3%) female, this is because the majority of patients were male expatriates seeking residency for work and littlies are Kuwaitis (17.7%). Also, the social characteristics of shepherds, the occupational group most at risk for brucellosis both through direct contact with herds and consumption of raw milk is interesting to consider. Bangladeshi males have almost exclusively run this occupation (Adel et al., 2001). As a result, the male to female ratio, which was 2:1 in 1985 (Lulu et al., 1988), has now changed to 4.8:1. The relative social isolation of these patients is reflected in the fact that, when sick, they tend to stay longer in the hospital than other non-Kuwaiti groups.

The reduction of the occupational exposure to brucellosis in shepherds should be an important preventive issue towards the elimination of brucellosis as a human infection in Kuwait. To do so, more care should be given to the harsh conditions under which these shepherds operate, as they are often neglected and left to their own devices under very difficult conditions for many days. Providing better food and hygiene structures to the shepherds would certainly decrease their risk for brucellosis.

Some investigators had reported more severe forms of the disease in women (Zaks et al., 1995; Lifeso et al., 1985), but this finding had not yet been confirmed in our study.

Brucellosis is widely recognized as an occupational risk among adults (Young, 2000). However, in our study only 16.4% (25 farmers, seven laboratory personnel, and four veterinarians) had occupational risk. The main mode of transmission in our patients was the ingestion of unpasteurized milk and milk products (87.3%).

Similar to Gotuzzo's et al. (1987), our series had many patients who were from the same family (13.2%). We have also confirmed his observation that osteoarticular brucellosis occurred less frequently in individuals with brucellosis in their family, probably because family cases could be diagnosed and treated earlier.

The disease affects mainly organs rich in reticuloendothehal cells, with the musculoskeletal system being the most frequent target site (Colmenero et al., 1996; EJ Young et al., 2000). In our series, osteoarticular complaints were the most common symptoms and were more frequently encountered in acute than in the subacute and chronic stages. This is consistent with most of the published results (Yetkin et al., 2006; Al Dahouk et al., 2006; Crosby et al., 1949).

Routine laboratory data reported in most studies had been of little diagnostic value (Crosby et al., 1949). Reportedly, the erythrocyte sedimentation rate is of minimal diagnostic value in brucellosis (Agnew and Spink, 1949, however, the main hematologic abnormalities observed in our 220 patients were elevated erythrocyte sedimentation rate, anemia, elevated serum C-reactive protein, and elevated transaminases levels.

The incidence of spondylitis reported in the literature varies significantly, ranging from 6% to >50% (Young, 1995; Ariza et al., 1985; Mousa et a., 1987). Twenty one cases (9.5%) of our 220 patients exhibited spondylodiskitis. In accordance with the literature (Serre et al., 1981; Ariza et al., 1986), we found that the lumbar spine was the most frequent site of spondylodiskitis (33.3%). The cervical spine was the region least affected with this condition (14.3%). Brucella spondylitis usually affects persons in the fourth to sixth decades of life (Mousa et al., 1988; Nas et al., 2001). The mean age of the patients with spondylitis in our study was 52.2 ±9.6 years.

In cases of brucellar spondylodiskitis, initial radiographs may show completely normal findings, and early diagnosis is often difficult because of the long latency period with spondylodiskitis (Harman et al., 2001). MRI is the most suitable modality for evaluation of infectious spondylitis. It is more sensitive than other imaging modalities for detecting presence and extent of such infections.

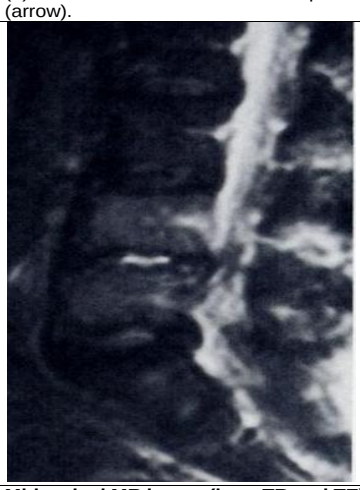
RECOMMENDATIONS

The magnitude of human Brucella infection in Kuwait can serve as a barometer of the prevalence of the disease in domestic animals. Eradication of brucellosis

Lateral radiograph of the lumbar spine:
(1) Loss of disk height at L4-5 and L5-S.
(2) Intradisk gas at L4-5 (arrow).
(3) Anterior osteophyte formation (arrowhead).

Fat-suppressed Ti-weighted MR image: (1) Focal enhancement of the anterior aspect of the superior end plate of L-3, L-4, and L-5.
(2) Enhancement of the anterior aspect of the L-4 and L-5 disks (arrow).

Midsagittal MR image (short TR and TE): Decreased signal intensity in L-4 and L-5.



Midsaginal MR image (long TR and TE):
(1) Diffuse high signal intensity of the bodies of L-4 and L-5.
(2) High signal intensity of the intervening disk.

in animals is the key to prevention in humans. Attempts to eliminate brucellosis had been successful in many developed countries. These countries maintain their brucellosis-free herds by serologic testing, quarantine, and other precautionary measures at their frontiers to prevent importation of infected animals (Hafez, 1986).
Human brucellosis acquired from milk is preventable, and legislation should be enacted to strictly require pasteurization of milk and dairy products. Nevertheless, public health education assumes an important role in preventing the transmission of brucellosis from animals to humans. (figure 1)

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