# Brucellosis in children of Dhofar region, Oman

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## ABSTRACT

**Objectives:** To study the epidemiological and clinical pattern of brucellosis in children of Dhofar and to ascertain the efficacy of a pre-determined antibiotic regimen to treat the disease.

**Methods:** The study was hospital based and was carried out prospectively for 3 years. All cases diagnosed to have brucellosis on clinical and serological basis were entered into the study. The epidemiological background and clinical presentations were analyzed and the clinical response to a combination of oral rifampicin and co-trimoxazole was evaluated.

**Results:** Three hundred and seventy five cases of brucellosis were eligible for the study. Ingestion of raw milk and its products were responsible for causation of the disease in 63% of cases. Eighty three per cent had direct contact with animals mainly cattle. A minority of 4.5% denied ingestion of raw milk or coming into direct contact with animals. Fever was the most common presenting feature at 91%. We identified 2 distinct groups of presentation: Seventy per cent of those who presented with arthritis belonged to the older age group (7.34 years, standard deviation 2.64). They did not have a systemic illness. The younger age group presented with severe systemic illness associated with severe leucopenia and thrombocytopenia. The clinical response to the combination of rifampicin and co-trimoxazole was satisfactory in 90% of patients and 98% of brucella species isolated from the blood of patients were sensitive to both antibiotics used.

**Conclusion:** Ingestion of infected milk and contact with infected animals are the main causes of human brucellosis, although aerial transmission from contaminated environmental soil could not be excluded. The main clinical presentation of brucellosis in children is fever but the skeletal manifestations of the disease are significant. The hematological manifestations of the disease in endemic areas deserve special attention. The combination of oral rifampicin and co-trimoxazole for 6 weeks is adequate to treat most cases of brucellosis in children.

**Keywords:** Human brucellosis, children, clinical, management.

**Saudi Med J 2001; Vol. 22 (7): 610-615**

Brucellosis is a zoonotic disease of major economic and public health significance.[1] Despite the growing number of countries declared brucella free, the disease remains widespread in many parts of the world.[2,3] The prevalence is highest in the Mediterranean countries, Central and South America, the Middle East and South Asia.[4-8] The reported incidence of human brucellosis in countries of the Arabian Peninsula is very high. In Saudi Arabia the incidence was estimated to be 80 cases per 100,000 population per annum.[2] In the State of Kuwait it was 85 cases per 100,000 population per annum.[9] The seroprevalence rate in Yemen Republic was estimated to be 0.5%.[10] This is low compared to that of the Kingdom of Saudi Arabia, 9%-27%.[11,12] Brucellosis in Oman is encountered mainly in the Dhofar region where the population is approximately 200,000. Ninety five per cent of cases in Oman are generally reported from this region. The incidence

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Received 24th July 2000. Accepted for publication in final form 18th March 2001.

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rate has been consistently above 100 cases per 100,000 population per annum.[6,13] Most cases occur in the coastal, mountainous areas falling in the monsoon belt. The seroprevalence among the indigenous camels was found to be 8%, goats 6.5% and cattle 3.5%.[14] In Dhofar, brucellosis is transmitted from animals to humans in ways similar to those described in the Kingdom of Saudi Arabia[15] and the State of Kuwait.[9] This includes the habit of consumption of raw milk and raw liver, close contact with animals at the time of their breeding, birth and slaughtering, and inhalation of contaminated dust. It is a local belief here that the boiling of camel milk, in particular, will spoil its taste. Another practice prevalent here is blowing by mouth into the vagina of the aborting cow to promote healing.

The diagnosis of brucellosis is often made on clinical grounds and confirmed by serological tests. The standard agglutination test (SAT) depends on the in vitro addition of brucella antigens to the patient's serum and looking for agglutination. It takes place in the presence of either, or both, immunoglobulin M (IgM) and immunoglobulin G (IgG). However, IgM is produced in the acute phase and it persists while IgGs appearance follows and it disappears from serum after some days. In case of re-infection IgG rises in serum. If 2 mercaptoethanol (2ME) is added, it will destroy the IgM bonds and the agglutination demonstrated will represent IgG and denotes re-infection.[16] The organism grows very slowly in vitro and blood culture is often negative.[16-18]

Antibiotic treatment of brucellosis takes at least 6 weeks as the organism localizes intracellularly in the reticuloendothelial cells of the host, a site that is relatively inaccessible to antibiotics.[7,19] A combination of rifampicin with tetracycline/ doxicycline is preferred for children above the age of 7 years, whereas rifampicin with co trimoxazole is considered suitable for younger children.[7,19,20] The objectives of this study were to describe the epidemiological and clinical features of brucellosis in the pediatric population, to assess the response of patients to a predetermined antibiotic regimen, its duration and the need to hospitalize patients for its administration. The study was hospital based and was carried out prospectively over a period of 3 years in Sultan Qaboos Hospital, which is a referral hospital for the Dhofar region.

**Methods.** All patients less than 13 years old whose diagnosis was brucellosis during the study period were included in the study. The diagnosis was based on clinical grounds[3] and confirmed as per the World Health Organisation (WHO) case definition criteria.[6] That definition required either a positive blood culture or a SAT titer of 1:160 or more. The SAT titers were determined as described by Mayer[18] using commercially available brucella antigens (Wellcome Diagnostics, Dartford, United Kingdom). The 2ME test was also carried out, in order to identify recent infections, by the addition of 2ME to the test sample followed by the SAT test. At least one sample of blood was collected for culture from each patient and it was incubated for a minimum of 21 days. Some had repeat cultures on follow-up. Cerebrospinal fluid (CSF) was cultured for 6 patients suspected of suffering from neurobrucellosis. Blood and CSF samples were innoculated into bottles of trophic soy broth and thioglycolate, and later subcultured on duplicate blood agar plates incubated with carbon dioxide ($CO_2$). Brucella isolates were identified by morphology, gram-reaction and slide agglutination using nonspecific *Brucella abortus* and *Brucella melitensis* antisera (Wellcome Diagnostic, Dartford, United Kingdom). Antibiotic susceptibility tests were carried out using the Stokes disc diffusion method[21] with Isosensitest Agar (Oxford, United Kingdom). All patients had complete blood counts and renal function tests. Liver enzymes and radiographs were carried out when indicated. Patients were generally treated as outpatients. They were admitted for inpatient care only if they: 1. Were aged less than 5 years, 2. Had rectal temperature of more than 39$^{o}$C, 3. Had arthritis that prevented weight bearing, 4. Failed to improve on oral medication or 5. Had non-compliance to oral medication at home.

The initial treatment for children less than 7 years old consisted of rifampicin 15mg/kg/day and co-trimoxazole (TMP/SMX) of 10/50mg/kg/day), given for 6 weeks. For older children doxycycline (4mg/ kg/day) was substituted for co-trimoxazole. Those who were very ill and toxic or those who failed to tolerate oral medication were in addition administered gentamicin (5mg/kg/day) for 7 days. The parents of children treated on an outpatient basis were advised to report back to the hospital in case of failure to administer medication or if the symptoms persisted for more than a week after starting therapy. Resolution of symptoms and normalization of temperature assessed the initial response to treatment. Patients were evaluated at 6 weeks to decide the need for further antibiotic therapy. Serology, erythrocyte sedimentation rate (ESR) and full blood count (FBC) were repeated at that time. Those who needed further antibiotic treatment were scheduled for another follow up visit at 12 weeks and again at 6 months. Their blood was taken for repeat culture. Four pediatricians were responsible for treating all brucella cases and filling of their clinical and laboratory details in the study questionnaire. This questionnaire contained detailed patient identification, presenting symptoms, clinical findings investigation and antibiotic treatment. Also, there were entries for follow up visits at 6 weeks, 3 months and 6 months where details of clinical findings and investigations, repeat SAT, 2ME and Erythrocyte sedimentation rate was recorded. This information is then entered into the WHO data and analysis program EPI Inf. Version 6. Statistical analysis was carried out using this computer program.

**Table 1** - The main clinical features of brucellosis in 375 patients.

| Features | n (%) |
|---|---|
| Fever | 340 (91) |
| Sweating | 212 (57) |
| Limb pain | 207 (55) |
| Single joint arthropathy | 150 (40) |
| Splenomegaly | 86 (23) |
| Backache | 74 (20) |
| Hepatomegaly | 68 (18) |
| Adenopathy | 44 (11) |
| Multiple joint arthropathy | 39 (10.5) |

**Results.** Three hundred and ninety patients were treated for brucellosis between September 1995 and September 1998. Fifteen patients were excluded due to poor records or refusal of investigations. Of the remainder, 152 were treated as inpatients and 223 as outpatients. Males were 201 (54%) and females were 174 (46%). The ages ranged from 7 months to 12 years with a mean age of 5.6 years (standard deviation (SD) 3.343).

***Clinical presentation.*** Fever presented in 340 patients (91%) sweating in 212 patients (57%) and limb pain in 207 patients (55%), Table 1. Temperature at presentation ranged from 38°C-40°C. Diurnal variation of temperature was not significant and 145 patients (97%) were febrile by the 4th day of admission to hospital. Sweating occurred with and without fever. Limb pain was associated with arthritis in 188 patients and 19 patients had arthralgia. Arthritis affected the hips of 128 patients (68%), the knees of 49 patients (26%) and the ankles of 11 patients (6%). Seventy per cent of those who presented with arthritis tended to belong to the older age group (mean age 7.34 yrs. SD. 2.64) as opposed to those who did not have arthritis (age 4.1 yrs. SD 1.9). They had less systemic illness and splenomegaly occurred in only 4%. Backache was mostly related to the lumbosacral region and it was not incapacitating to patients. Forty-one patients had variable lymphadenopathy, which was generalized in only 6 of them. Liver enlargement was moderate and so was the splenic enlargement. The maximum spleen size was 5 cm below the costal margin. Two patients presented with parotitis and 2 with hip dislocation due to excessive effusion. One patient each presented with cholecystitis, peritonitis and cerebellar ataxia. One patient had hematuria secondary to thrombocytopenia. Three hundred and eleven patients (83%) gave a history of direct animal contact including cattle, goats and camels. Raw milk was ingested regularly by 86 patients (23%) and occasionally by 150 patients (40%). Most patients (96%) stated that they cooked food very well before consumption. However, 16 patients (4%) denied a history of animal contact, drinking raw milk or ingestion of raw meat. They lived in the vicinity of animals. The mean duration of illness before presentation was 18 days (SD 9.61). Brucellosis was experienced and treated (within one year of presentation) by 7.5% of our patients and 40% had a family member who suffered from brucellosis.

***Laboratory findings.*** Fifty four patients had leucopenia (white blood cell count of <5000/UL) and 25 of them had counts <3000/UL. Among this latter group 10 patients had an absolute neutrophil count of <1500. These severely leucopenic patients also had significant thrombocytopenia, hepatosplenomegaly and systemic illness Table 2. Thrombocytopenia (<150000/UL) featured in 15% of the whole group

**Table 2** - Differentiating clinical and laboratory findings in inpatients who had leucopenia compared to the rest of the in patients.

| Variable | Patients with WBC <3000/ul (n=25) | Patients with WBC>3000/ul (n=127) |
|---|---|---|
| Mean age (Years) | 4.5 (SD=2.25) | 5.7 (SD=3.81) P<0.05 (SE=0.42) |
| Splenomegaly (%) | 64 | 39 P<0.05 (Chi sq=4.4) |
| Hepatomegaly (%) | 48 | 24 P<0.05 (Chi sq=5.05 |
| Arthritis (%) | 36 | 63 P<0.03 (Chi sq=5.4) |
| Positive blood culture (%) | 64 | 31 P<0.05 (Chi sq=4.11) |
| Hemoglobin (gm/uL) | 12.72 | 13.64 |
| Platelets (X10/uL) | 125 | 186 |
| ESR (mm/1st hour) | 34.2 (SD=15.6) | 38.6 (SD=18.5) P>0.05 (SE=4.63) |
| AST (IU/L) | 96.2 | 88.4 |
| ALP (IU/L) | 108 | 98.6 |
| ALT (IU/L) | 88.1 | 76.3 |

ESR=erythrocyte sedimentation rate, AST=aspartate transaminase, ALP=alkaline phosphatase ALT=alanine aminotransferase, WBC=white blood cell, SD=standard deviation, SE=standard error, P=p-value, Chi sq=Chi square

and the counts for 2 patients were 38000 and 5000/UL. The ESR was <20mm/1st hr in 21% of patients. It was 20-40 mm in 56%, 41-60 mm in 38% and >60mm in 9% of patients. The results of the initial serological tests carried out are shown in Table 3. The SAT titers were very high >1:1280 in 57% of patients and there was no association of the titer level to any special clinical presentation. Those who were treated previously for brucellosis 7.5% had SAT titers similar to the rest of the group but 85% of them had positive 2ME tests. Organism isolation rate from blood was 38%. Sixteen out of the 25 severely neutropenic patients had positive blood culture 64%. *Brucella mellitensis* was isolated from blood of 74% and in the remainder it was *Brucella abortus*. All isolates were sensitive to tetracyclines, doxycyclines and ciprofloxacin. Sensitivity was 98% to rifampicin, co-trimoxazole and streptomycin.

***Antibiotic treatment.*** All patients were started on the combination of rifampicin and co-trimoxazole, but 3 were also administered gentamicin due to persistent vomiting soon after initiation of oral treatment. Later, we also had to add gentamicin to the treatment of 13 patients due to their poor compliance or intolerance to the oral medication. According to the age criteria we gave doxycycline instead of co-trimoxazole to 15 patients. We did not encounter any serious side effects to antibiotics and 330 patients (90%) were satisfactorily treated with antibiotics for 6 weeks. Twenty two patients (6%) needed to continue treatment for 12 weeks. All of them had musculoskeletal disease without osteomyelitis. Two patients were treated for 6 months and both had persistent arthritis of the hip. None of those who were treated for more than 6 weeks grew organisms from their repeat blood cultures. Fifteen patients were lost in follow up.

**Table 3** - Serological results of all brucella cases initially (n = 375) and after 6 weeks of therapy (n =360).

| | **After therapy** n (%) | **After therapy** n (%) |
|---|---|---|
| **SAT titer** | | |
| Negative | 20 (5) | 248 (66) |
| 1:160 | 7 (2) | 61 (17) |
| 1:320 | 18 (5) | 27 (7.5) |
| 1:640 | 116 (31) | 25 (7) |
| >1:1280 | 214 (57) | 14 (4) |
| **2ME SAT titer** | | |
| Negative | 76 (20) | 281 (78) |
| 1:160 | 110 (29) | 40 (11) |
| 1:320 | 98 (26) | 26 (7) |
| 1:640 | 65 (17) | 9 (2.5) |
| >1:1280 | 26 (7) | 4 (1) |

SAT=standard agglutination test, 2ME=2 mercaptoethanol

***Follow up.*** On the initial outpatient department follow up at 6 weeks of antibiotic therapy 367 patients 98% were seen. Three hundred and forty 93% were asymptomatic. The ESR was carried out for 348 follow up patients and it was <20 mm/1st hour in 61%. The remainders had ESRs of less than 40 mm/ 1st hour. The SAT titers were repeated for 360 patients. They were 1:160 or less in 86% of them. The 2ME titers were significantly low, (Table 3). Also the clinical response of the 150 inpatients was good. Fever came down in 145 of them (97%) by the 4th day of admission. By that tme arthritis had resolved in 71 out of the 89 arthritic patients 80%. The mean duration for hospital stay was 6.8 days (SD 2.44). We continued to follow our patients and none of them had relapse during the last 2 years following the study.

**Discussion.** Brucellosis appears to be the most important public health problem in our region. It caused no mortality but it creates significant morbidity especially among school going children. Despite their awareness people in our study were not willing to abandon the drinking of raw milk as a local custom. This is especially so with respect to camel milk due to a common belief here that boiling spoils its taste. It is of note that a fair number of patients 4% contracted the disease without evidence of ingestion of potentially infectious material or direct animal contact. Some of them might have denied or played down the importance of occasionally taking small amounts of raw milk. For the remainder we can explain this only by environmental exposure since they lived in the vicinity of animals. The role of environmental exposure has become increasingly important in causation of brucellosis.[6,12,20] The overall clinical presentation is similar to what has been stated by others.[1,7,8,18] Fever and sweating were the main presenting symptoms as has been reported from the Kingdom of Saudi Arabia[7] and the State of Kuwait.[8] Hip involvement in brucellosis is well described[22-24] but it was very striking in our study. It is similar to the findings of Benjamin & Khan of the Kingdom of Saudi Arabia.[25] The monoarticular presentation was so common that at times we thought we were underdiagnosing septic arthritis. The low WBC count and the normal or low ESR weighed against the diagnosis of septic arthritis. However, apart from joint effusion in 3 patients and hip dislocation in 2, we did not encounter long term skeletal complications. Dislocation of the hip was reported in 4 patients within a series of 190 patients from the Kingdom of Saudi Arabia[25] but none was reported from a similar study in the State of Kuwait of both hip and knee arthritis.[23] Most of the backache in our series was on the lumbosacral region. We believe it was due to involvement of the sacroiliac

joint but we did not carry out bone scans to document it. Our hematological findings are in keeping with the observations of Shalev et al.[26] Previous reports stated that hematological presentations are rare in children.[27] A number of mechanisms have been implicated in the pathogenesis of pancytopenia in brucellosis. Among these are bone marrow granulomas, hypersplenism, hemophagocytosis, peripheral or marrow immune destruction and marrow hypoplasia.[7,28-30]

We noted with interest the emergence of 2 groups in our study: those who presented with arthritis and tended to belong to the older age group and have little systemic illness. The other ones were the leucopenic, thrombocytopenic patients of younger age and more systemic illness. Young[31] referred to these groups with the term localized presentation for the former and systemic presentation for the latter, but he did not identify them as distinct entities. It is difficult to make conclusions on this matter but we think that our observation needs attention and verification by others. Serology was the main diagnostic tool in our series. As shown in Table 3 the initial SAT titers were very high >1:1280 in 57% of patients probably due to repeated infections. It has been the observation of others that chronic patients have high antibody titers.[32] The 2ME test was positive for most of those who had the systemic illness presentation. They mainly had acute presentation and therefore most of their antibodies were IgG. Some of them presented even earlier than the time of showing a positive 2ME test corresponding to the initial rise of IgM in the course of the illness. They were diagnosed by positive blood cultures. The SAT titers of these patients at follow up were occasionally higher than the initial titers. In fact many of our SAT titers were still high at the initial follow up due to starting with very high titers, but they fell in subsequent follow up. This observation agrees with others[33,34] who stated that brucella antibodies remain measurable for a long time after treatment which makes it difficult to separate chronic brucellosis from relapse. The 2ME test was most useful to us to make the distinction. Our isolation rate of 38% compares well with others findings.[35,36] *Brucella melitensis* seems to have established itself in sheep, cattle and camels. This is in support of the findings of the Kuwait study on the subject.[9] Also it has been observed by others that childhood brucellosis is more commonly associated with melitensis species.[37] In addition camels are an important reservoir for brucellosis in Oman[14] and our patients consumed raw milk from camels more often than from other animals. Our decision on the antibiotic regimen was based on others' experiences[9,20,36,38,39] and was later supported by our own bacteriologic findings. We avoided streptomycin due to intamuscular injections not being popular here. We also used gentamycin sparingly (to avoid its potential side effects) to shorten the duration of hospital stay.

Most of our patients 90% responded to the 6 weeks treatment period. In very few occasions (6%) it was necessary to exceed 12 weeks. This we took as treatment failure and it is comparable to what was found in a multicentre studies on the subject.[19,40,41] Follow up of our patients is still ongoing and we have not had any relapse from our study group.

The presentations of parotitis, peritonitis and cholycystitis were noteworthy though not surprising in our large series as no organ is immune to this disease. Al-Eissa from the Kingdom of Saudi Arabia reported cases of congenital brucellosis[42] and breast milk bone disease,[43] but we did not see any such case. Our breast fed infants who suffered brucellosis (2 cases) were also given raw cows milk. We diagnosed only one case of neurobrucellosis (cerebellar ataxia) which does not compare with the incidence figures of 2-5% in studies of others.[44,45]

In conclusion we have shown that brucellosis is an important public health problem in this area and there is a need for raising the public awareness regarding its seriousness. *Brucella melitensis* was mainly responsible for the disease. The clinical presentation is similar to what has been described before, but 2 clinical entities of the disease are stressed in our study: one akin to septic arthritis and the other mimicking reticuloendothelial malignancy. Standard agglutination test suffices as the main diagnostic test and the 2ME test is helpful at times to differentiate between acute and chronic infections. The combination of rifampicin and co-trimoxazole for 6 weeks duration is suitable for treatment of most patients and there is no need for routine admission of these patients.

**Acknowledgment.** We are grateful to Dr Kamal El-Haj, Head of Department of Microbiology, Royal Hospital Muscat, Sultanate of Oman for his meticulous review of the manuscript and subsequent advice.

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