Original Report

Brucellosis in children: clinical observations in 115 cases

Mohammed Al Shaalan,[1] Ziad A. Memish,[2,3] Suleiman Al Mahmoud,[3] A. Alomari,[1] Mohammed Y. Khan,[4] Maha Almuneef[1,2] and Suleiman Alalola[1]

Objective: Brucellosis is endemic in Saudi Arabia. This report summarizes the epidemiology of brucellosis in children.

Method: A retrospective review was made of medical records of all patients admitted to King Fahad National Guard Hospital with brucellosis during the period from 1984 to 1995.

Results: Children ≤12 years constituted 115/545 (21%) of the total brucellosis admissions. The mean age was 5.8 years and 64% of the patients were males. Consumption of unpasteurized milk (often from camel) was the main source of infection. In 70% the clinical picture was dominated by arthritis, 20% of patients presented with a non-specific febrile illness without localizing signs, and 10% had a febrile illness with uncommon presentations. Brucella serology was most helpful in making an early diagnosis. Initial titers of >1:640 were found in 90% of the cases. Bacteremia was observed in 45% and of the isolates speciated, 96% were *Brucella melitensis*. No increase in resistance to commonly used antimicrobials was noted during the 12-year study period. A combination of rifampin plus co-trimoxazole with or without streptomycin was used in two thirds of the patients. The overall rate of relapse was 9% and one patient died from neurobrucellosis.

Conclusion: Brucellosis presents in various ways and should be included in the differential diagnosis of arthritis in endemic countries. Prevention should rely on education including on boiling raw milk.

Int J Infec Dis 2002; 6: 182–186

In Saudi Arabia, brucellosis is an endemic zoonotic disease.[1–4] Although it is believed that children are uncommonly involved, a number of reports from endemic areas showed a higher percentage of children involved (20–30% of affected patients).[5,6] Clinical manifestations of childhood brucellosis are varied ranging from minimal symptoms to extreme morbidity and occasional fatality. Asymptomatic infections are also not uncommon.

The fact that brucellosis is endemic in the Kingdom became clearer in the early 1980s. Several reasons have been considered but the most prominent of them is the increase in the importation of animals from areas where brucellosis is endemic, especially some African countries. Consumption of raw milk and to a lesser extent contact with infected animals or their products are the main routes of infection. The consumption of fresh, unpasteurized milk from camels is a traditional practice, and people believe that boiling removes the goodness from the milk.

[1]Department of Pediatrics; [2]Department of Infection Prevention and Control; [3]Department of Internal Medicine, King Fahad National Guard Hospital, Riyadh, Saudi Arabia; [4]Department of Internal Medicine, Maricopa Medical Center, Phoenix, USA.

Address correspondence to Ziad A. Memish, MD, CIC, FACP, FRCPC, FIDSA, Chief Adult, Infectious Diseases and Executive Director, Infection Prevention and Control program, NGHA, King Fahad National Guard Hospital, P.O. Box 22490, Riyadh 11426, Saudi Arabia. E-mail: memish@ngha.med.sa

Corresponding Editorial Office: New York

This review was made to clarify the epidemiology, clinical features, and response to therapy in selected children in Riyadh City, the capital of Saudi Arabia.

MATERIALS AND METHODS

King Fahad National Guard Hospital (KFNGH) serves a large population of Saudi National Guard Soldiers and their extended families. Many of these individuals live traditional life styles in close association with livestock such as sheep, camels, and goats. The consumption of raw milk from animals, in which the incidence of brucellosis is high, is a cultural norm.

A retrospective review was made of all patients admitted to KFNGH with brucellosis from 1984 to 1995. Patients included were those ≤12 years of age and who had clinical features suggestive of brucellosis and serum agglutination titre (SAT) for brucella of >1:160, and/or positive blood or body fluid culture for *Brucella* spp. From 1983 to 1985, blood and other sterile body fluids were cultured in tryptic soy broth and Thiol broth bottles (Difco Laboratories, East Molesey, United Kingdom). If growth developed (or routinely if no growth was observed), subculturing was done onto chocolate agar, blood agar, and enriched modified blood agar for anaerobes. For initial cultures, CO_2 was used, but further testing did not require CO_2. If brucellosis was indicated in the differential diagnosis, the culture was held for three weeks before being discarded; routine subculturing was done at weeks two and three. In 1986, the laboratory began to use the BACTEC 660 system

Table 1. Brucellosis in children – 115 cases: presenting symptoms and physical findings

Symptoms and physical findings	*No. of patients (%)*
Symptoms	
fever	101 (87.8)
arthralgia/arthritis	84 (73.0)
chills	21 (18.2)
malaise	21 (18.2)
excessive sweating	10 (8.6)
headache	8 (7.0)
miscellaneous	7 (6.0)
Physical findings	
fever	105 (91.3)
arthritis	82 (71.3)
hepatomegaly	15 (13.0)
splenomegaly	14 (12.1)
neck stiffness	3 (2.6)
miscellaneous*	8 (7.0)

Skin rash=2; cervical nodes=2; drowsiness=2; periorbital swelling=1; ataxia=1.

Table 2. Brucellosis in children – 115 cases: febrile illness with uncommon findings

Uncommon findings	*No.*
Neurobrucellosis	3
Thrombocytopenia	2
Acute abdomen/diarrhea	2
Pneumonia	1
Myocarditis	1
Nephritis	1
Hepatitis	1
Myelodysplastic syndrome	1
Total	12

Table 3. Brucellosis in children – 115 cases: routine laboratory findings

Laboratory test	*No. tested*	*Percent abnormal*
Leukopenia (< 5000×10^b/L)	115	9.5
Leukocytosis (>$10,000 \times 10^b$/L)	115	22.6
Monocytosis	115	22.6
ESR (> 25 mm/hr)	88	73.8
Anemia	115	25.0
LFT (SGPT, bilirubin)	49	18.3

Table 4. Brucellosis in children – 115 cases: serology (initial titer)

		Positive culture	
Titer	*No. of patients*	*Blood*	*Other sites*
Not done	2	1	1*
Titer ≤1:80	1	1	0
Titer ≤1:160	0	0	0
Titer ≥1:320	112	38	3
Total	115	40	4

*Positive CSF and peritoneal fluid (VP shunt infection).

(Becton-Dickinson, Towson, Maryland) for initial blood cultures with subculture onto enriched media and speciation by biochemical methods: CO_2 requirement, urease activity, and growth on basic fuchsin and thionin dyes. In 1995, the BACTEC 660 system was replaced by the BACTEC 9240 system for initial blood cultures with subculturing onto chocolate blood agar at 37°C in CO_2. Antimicrobial susceptibility testing was performed by broth dilution.[7,8]

The species of brucella was determined by standard biochemical methods. The species of some isolates were not discovered because of shortage of reagents from time to time. Brucella SAT was performed using a microtiter agglutination procedure with *B. abortus* and *B. melitensis* antigens (stained *B. abortus* SS14 and *B. melitensis* SS15 suspensions, containing approximately 1010 organisms/ml; Wellcome Diagnostics, Dartford, England). Cook microtiter plates were used to receive specimens and controls. Each serum was diluted from 1:80 to 1:20,480, which overcomes the prozone phenomenon. Each batch of tests included a positive 1:1280 and a negative saline control.[9]

RESULTS

One hundred and fifteen children ranging in age between 6 months and 12 years were included. This represents 1–8/1000 of children discharged through 1995. The highest incidence was noticed in 1987 and 1988. Gender distribution showed male predominance (74 [64.3%] patients were males). Eighty five percent of patients had history of raw milk ingestion and 47% had a family history of brucellosis. The presenting symptoms and clinical signs are shown in Table 1. Most (76%) of the patients presented within the first two weeks of their illness. The most common presenting symptoms included fever in 87.8%, followed by arthralgia/arthritis in 73% of patients. Physical findings on presentation included fever in 91.3%, arthritis 71.3%, and hepatomegaly and splenomegaly in 13% and 12% respectively.

Most patients (76%) presented with acute symptoms of no longer than 2 weeks duration, while 10 patients (8.7%) had a chronic presentation with symptoms before hospitalization of more than 6 weeks; 18 (15.6%) had subacute presentation >2 weeks to <6 weeks. There were three categories of clinical presentations: arthritis and fever were the commonest symptoms occurring in 82 patients (71.4%), followed by nonspecific febrile illness in 21 patients (18.2%); 12 patients (10.4%) presented with fever and variety of other uncommon presentations listed in Table 2.

The most commonly involved joint with arthritis was the hip joint in 40 patients (40.8%), followed by the knee, ankle, elbow, sacroiliac, and wrist joints in 39.7%, 10.7%, 4.3%, 3.2%, and 1.0% respectively. Monoarthritis was more common than polyarthritis: 90% vs 10%. All patients who had arthritis recovered

fully without sequelae. Osteomyelitis was present in 8.5% of patients.

Routine laboratory findings are shown in Table 3. Leukocytosis (>10,000 10^b/L) was seen in 22% of the 115 patients tested, however, none of our patients had a white blood cell count of >20,000 10^b/L. Leukopenia (<5000 10^b/L) was seen in 9.5% of the 115 patients tested. Anemia (Hgb <10 g/dL) was seen in 25% of the 115 patients tested. The ESR was considered high (>25 mm/h) in 73.8% of the 88 patients tested. Raised liver function tests was seen in 18.3% of the 49 patients tested. Among 89 blood cultures obtained, 40 (45%) were positive for brucella. Synovial fluids were less likely to be positive: three out of 15 (20%) cultured synovial fluids were positive. Only one patient had a positive CSF culture. This was a 2-year-old child who had Dandy–Walker disease (this includes obstruction of the outlet foramina of the fourth ventricle, which becomes massively dilated and hydrocephalus results from the obstruction of the CSF). A ventriculoperitoneal shunt was inserted early in life. This patient was admitted with fever and abdominal distention. CSF from the shunt tap and the ascitic fluid grew *Brucella* species. The *Brucella* titer was 1:160 for *B. abortus* and 1:320 for *B. melitensis*. The blood culture was negative.

Among the 27 isolated brucella strains, 26 (96%) were *B. melitensis* and one (4%) was *B. abortus*. The SAT result is shown in Table 4: 90% had a titer >1:640. In two patients, SAT was not done and one patient had a titer < 1:80. All these patients had positive blood cultures. Susceptibility tests were performed on 42 of 44 isolates and the results are shown in Table 5. Only eight isolates (19%) were resistant to co-trimoxazole (trimethoprim/sulfamethoxazole (TMP/SMZ) and three isolates (7%) were resistant to rifampin. No strain was resistant to tetracycline or streptomycin. There was no increase in the resistance noted over the years of the study. Various regimens of therapy were used as shown in Table 6. A combination of rifampin and co-trimoxazole with or without streptomycin was used in two thirds of the patients. The remaining one third received streptomycin plus tetracycline with or without rifampin or co-trimoxazole. Ninety eight patients had a complete therapy and follow up; 89 had complete recovery and eight (9%) relapsed after stopping therapy. One patient with neurobrucellosis died. Follow up was for >1 year for all patients.

Table 5. Brucellosis in Children – 115 cases: Antimicrobial Susceptibility Data (Susceptibility Performed on 42/44 Isolates (95%)

Antimicrobial	*No. resistant*	*Percent resistant*
Co-trimoxazole	8	19
Rifampin	3	7
Streptomycin	0	0
Tetracycline	0	0

No increase in resistance noted over the 1983–1995 study years.

Table 6. Brucellosis in Children – 115 Cases: Treatment Regimens

Regimen	*No. of patients*
Streptomycin+co-trimoxazole+rifampin	35
Streptomycin+co-trimoxazole	27
Rifampin+co-trimoxazole	15
Streptomycin+tetracycline	14
Streptomycin+tetracycline+co-trimoxazole	8
Streptomycin+doxycycline+rifampin	6
Other combinations	9
No therapy	1
Total	115

DISCUSSION

Brucellosis is endemic in Saudi Arabia with a seroprevalence of 15%.[2] Childhood brucellosis is common in our population. Among 545 cases that were reviewed over a 12-year period, 115 cases (21%) were children. In a seroprevalence study in Saudi Arabia carried out in 1997, it was found that 9.7% of surveyed children <15 years of age were seropositive.[2] Previous reports from the Kingdom showed a similar trend.[1,4] The highest incidence was noticed during the years of 1987 and 1988 at which time the disease was highly endemic in the kingdom. Brucellosis symptomatology is very variable, in part because of the variable pathogenecity of different strains. It is known that *B. abortus* causes milder disease with either mild symptomatology or focal lesions. However, infection with *B. melitensis* is usually associated with a high rate of bacteremia, short incubation periods, and noticeable symptoms. This was seen in our patients; 76% presented within two weeks of onset of their symptoms. This observation is in agreement with previous reports.[1,5] Arthralgia/arthritis and fever were the most common presenting combination of symptoms. Fever and arthritis were the most common presenting signs. Monoarthritis was more common than polyarthritis. This may create confusion with pyogenic arthritis in children; therefore in a community where brucella is common, awareness about this entity should prompt investigation for this disease, and physicians should have a high index of suspicion for brucella arthritis. The most commonly affected joints were hip and knee. Unlike in adults, the sacroiliac joint and axial skeleton were rarely affected. Brucella osteomyelitis is rare in children. Previous series showed that only 1–2% of children with brucellosis have osteomyelitis; however, our study showed an 8% rate.[1,5] This could be attributed to an increase in the use of radioisotopic imaging studies. Brucellosis can cause this disease in areas where it is endemic. Almost any organ can be affected and varied complications are being reported.[10–17] In this series 10.4% of the affected children had a febrile illness with uncommon presentations. Three children had neurobrucellosis; one of them presented with abdominal distension. This child had a ventriculoperitoneal shunt and his neurobrucellosis manifested as peritonitis and

ascites. A similar presentation was reported in a lady who had a ventriculoperitoneal shunt inserted for increased intracranial pressure, which in retrospect was found to be due to brucellosis after brucella was isolated from ascitic fluid. Neurobrucellosis is rare in children and it has been reported in only 0.5–1% of children with brucellosis.[12–14] Most of the affected children present with acute meningitis or meningoencephalitis. Recovery is usual and sequelae are rare. Hematological abnormalities are not uncommon in brucellosis. In our series 25% of patients tested had anemia. Similar findings have been reported by others.[1,5] Leukocytosis was seen in up to 25% of our patients. Lymphocytosis is prominent in the differential count, occurring in 70%. Other studies have shown variable results with some reporting lymphopenia and some reporting lymphocytosis.[1,5] Thrombocytopenia is seen less frequently and is usually mild; however, severe thrombocytopenia has been reported.[11] Two of our patients had severe thrombocytopenia (<50,000), which recovered after 10 days of initiating antibrucella therapy. Several mechanisms have been entertained for these hematological abnormalities. These include bone marrow suppression, peripheral destruction, hemophagocytosis, as well as immune mechanisms.

Although positive culture should be the gold standard for diagnosis, its yield remains suboptimal. Most studies have shown a 40–50% yield. Culture in biphasic medium (Castaneda method) and lysis concentration have been recommended to improve the recovery of brucella.[18] Rapid diagnosis of brucella using the automated system of nonradiometric BACTEC or BACT/ALERT has shown a better and faster recovery.[7,19] Because of the lower yield of culture, SAT remains the best diagnostic modality available. In endemic areas there may be a persistent and continuing exposure to the source of infection, and therefore there may be a persistent low titer in the range of 1:160–1:320 in the absence of true infection.[9] In these areas a titer of 1:640 or higher is a good predictor of the presence of the disease. Our study showed that 92% of children with acute brucellosis have a titer of 1:640 or more. Coupling SAT with the 2-mercaptoethanol agglutination test is useful in differentiating acute from chronic brucellosis. The 2-mercaptoethanol agglutination test elutes IgM out leaving IgG. Elevated IgG titers indicate an acute disease. A negative 2-mercaptoethanol test after therapy indicates a good response to treatment. False negative SAT results also occur but are rare, as is shown in this study where only one patient had negative serology and positive blood culture. ELISA is a promising serological test and has shown to be of better sensitivity and specificity.[20]

The armamentarium of antibiotics for treating childhood brucellosis is limited. Available proven effective antibiotics include aminoglycosides, rifampin, and trimethoprim/sulfamethoxazole (TMP/SMX). Tetracyclines can be used for those who are >8 years of age. The most effective regimen includes a combination therapy given for four to six weeks.[1,21] Such combinations are usually TMP/SMX and rifampin, with or without streptomycin for two weeks or gentamicin for five days. Doxycycline can replace rifampin or TMP/SMX for children >8 years of age. Short duration therapies of <4 weeks have proven to be less effective.[1,22] However, one study showed that three weeks' duration therapy is as effective as five weeks and eight weeks of therapy.[23] In this study the standard of four weeks combination therapy was adopted, and only a 9% relapse rate was observed. In our population it is difficult to differentiate between relapse and reinfection as some of our patients continued to be exposed to the source of infection. Therefore this 9% relapse may be overestimated. The eradication of human brucellosis ultimately depends on the eradication of animal brucellosis. Although education of the public has been advocated as an alternative strategy to control disease in humans, it should be considered as an adjunct and not an alternative.[24]

ACKNOWLEDGEMENTS

The authors thank Dr. A. Kagalwala for help in the collection of data for this study. We would also like to acknowledge Professor Allan Ronald and Professor Noni McDonald for their critical review of the manuscript and valuable comments.

REFERENCES

1. Al-Eissa YA, Kembal AM, Al-Nasser MN, et al. Childhood brucellosis: A study of 102 cases. Pediatr Infect Dis J 1990; 9:74–79.
2. Al Sekait MA. Seroepidemiological survey of brucellosis antibodies in Saudi Arabia. Ann Saudi Med 1999; 19: 219–222.
3. Cooper CW. The epidemiology of human brucellosis in a well defined urban population in Saudi Arabia. J Trop Med Hyg 1991; 94:416–422.
4. Al-Marshedy A, Harland PS. Brucellosis in children. Ann Saudi Med 1986; 6:S25–S27.
5. Sharda DC, Lubani M. A study of brucellosis in childhood. Clin Pediatr 1986; 25:492–495.
6. Gottesman G, Vanunu D, Maayan M, et al. Childhood brucellosis in Israel. Pediatr Infect Dis J 1996; 15:610–615.
7. Bannatyne R, Jackson M, Memish Z. Rapid diagnosis of Brucella bacteremia by using BACTEC 9240 system. J Clin Microbiol 1997; 35:2673–2674.
8. Memish Z, Mah M, Almahmoud S, Alshaalan M, Khan MY. Brucella bacteremia clinical and lab-observation in 160 patients. J Infect 2000; 40:59–63.
9. Kiel FW, Khan MY. Analysis of 506 consecutive positive serologic tests for Brucellosis in Saudi Arabia. J Clin Microbiol 1987; 25:1384–1387.
10. Akdeniz H; Irmak H; Seckinli T; Buzgan T; Demiroz AP. Hematological manifestation of brucellosis cases in Turkey. Acta Med Okayama 1998 ;52:63–65
11. Benjamin B. Acute thrombocytopenic purpura in childhood brucellosis. Ann Trop Pediatr 1995; 15:189–192.

12. Lubani MM, Dudin KI, Araj GF, Manandhar DS, Rashid FY. Neurobrucellosis in children. Pediatr Infect Dis J 1989; 8:79–82.
13. Habeeb YK, Al-Najdi AK, Sadek SA, Al-Onaizi E. Pediatric Neurobrucellosis: Case report and literature review. J Infect 1998; 37:59–62.
14. Strannegard I, Araj GF, Fattah HA. Neurobrucellosis in an eight-year-old child. Ann Trop Pediatr 1985; 5:191–194.
15. Andersen H, Mortensen A. Unrecognized neurobrocellosis giving rise to Brucella melitensis peritonitis via a ventriculoperitoneal shunt. Euro J Clin Microbiol Infect Dis 1992;11:953–954.
16. Jubber AS, Gunawardana DR, Lulu AR. Acute pulmonary edema in brucella myocarditis and interstitial pneumonitis. Chest 1990; 4:1008–1009.
17. Lubani M, Sharda D, Helin I. Cardiac manifestations in brucellosis. Arch Dis Child 1986; 61:569–572.
18. Corbel MJ. Microbiological aspects of brucellosis. Saudi Med J 1993; 14:489–502.
19. Solomon HM, Jackson D. Rapid diagnosis of brucella melitensis in blood: some operational characteristics of BACT/ALERT. J Clin Microbiol 1992; 30:222–224.
20. Araj GF, Kaufmann AF. Determination by enzyme linked immunosorbent assay of immunoglobulin G (IgG), IgM, and IgA to Brucella melitensis major outer membrane proteins and whole-cell heat-killed antigens in sera of patients with brucellosis. J Clin Microbiol 1989; 27: 1909–1912.
21. Khuri-Bulos NA, Daoud AH, Azab SM. Treatment of childhood brucellosis: Results of a prospective trials on 113 children. Pediatr Infect Dis J 1993; 12:377–381.
22. Sanchez-Tamayo T, Colmenero J, Martinez-Cortes F, et al. Failure of short term antimicrobial therapy in chidhood brucellosis. Pediatr Infect Dis J 1997; 16:323–324.
23. Lubani MM, Dudin KI, Sharda DC. A multicenter therapeutic study of 1100 children with brucellosis. Pediatr Infect Dis J 1989; 8:75–78.
24. Memish Z. Brucellosis control in Saudi Arabia: Prospects and Challenges. J Chemother 2001; 13(Suppl 1):11–17.