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Osteoarticular brucellosis in children

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Abstract

The findings in 40 children (24 female, 16 male) with osteoarticular complications of brucellosis are presented. Raw milk was the main source of infection. Most patients had acute onset of fever, arthralgia, and myalgia. Arthritis was the presenting symptom in all patients, of whom two also had osteomyelitis. Arthritis was monoarticular in 28 (70%) of 40 cases with predilection for large weight-bearing joints. Spine and small joints were spared. *Brucella melitensis* was detected in 23/31 (74%) cases. Mild anaemia, leucopenia, increased liver enzymes, positive acute phase reactants, and low titres of autoantibodies were prominent non-specific laboratory findings. Bone scintigraphy was more helpful than conventional radiography in detecting hip and sacroiliac joint disease. Treatment with a combination of antibiotics for six weeks or more resulted in a cure rate of 92·5%. Early recognition of infection, prolonged treatment, and long term follow up should improve the outcome of patients.

Brucellosis constitutes a major health problem in many parts of the world, including the Middle East.[1] The disease due to *Brucella melitensis* is a common infection in domestic animals[2] and the human population in Saudi Arabia.[3–6] The recent surge in the incidence of brucellosis in that country has been linked to the widespread animal husbandry and the prevailing habit of ingesting raw milk or its products.[3 6]

Musculoskeletal involvement was first reported by Kennedy in the early part of this century.[7] Since then, there have been further reports from countries where the disease is common.[4–6 8–18] Bone and joint disease, which includes suppurative arthritis, spondylitis, and osteomyelitis, is considered to be the most common complication of brucellosis.[6 18] The reported prevalence of osteoarticular complications varies from 11% to 85% in the published series.[10 11] This variation has been attributed to differences in the pathogenicity of the infecting brucella species, with *B melitensis* producing the most serious illness, to differences in the host and environmental factors of the population studied, or to discrepancies in the diagnostic criteria.[14 18]

Previous descriptions of the osteoarticular pattern in patients with brucellosis have been based mainly on series of adult cases. In this report we describe the clinical presentations, laboratory and radiological findings, and the outcome of treatment in a group of 40 children with osteoarticular brucellosis.

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Subjects and methods

During the four year period between January 1985 and December 1988 106 children with brucellosis were seen at the King Khalid University Hospital; 40 (38%) of these (24 female, 16 male) with osteoarticular complications form the body of subjects of this study. Their mean age was 8·2 years (range 2 to 14). All were Saudi nationals and 29 (72·5%) of them were school age children. Of the 40 patients, 33 (83%) had previously consumed raw milk, 13 (33%) had close contact with domestic animals, and three (8%) had no clear exposure to a source of infection. The diagnosis of brucellosis was made on the basis of a clinical picture consistent with the disease and one or more of three laboratory criteria: isolation of the organism from blood or synovial fluid, or both; brucella agglutination of $\geq$1/160; and a fourfold rise in titres following the onset of symptoms.

All patients were admitted during their initial presentation to the hospital and the following studies were carried out for each patient: complete blood cell count, erythrocyte sedimentation rate (Westergren method); liver and renal function profiles, brucella titre (standard tube agglutination method using Wellcome stained brucella antigens); and urine analysis. Two blood cultures and, if indicated, synovial fluid cultures inoculated into bottles of tryptic soy broth and thioglycolate broth (Difco) were obtained from 31 patients. Antistreptolysin O titre (haemolysin test, normal <166 Todd units/l) was measured in 28 patients. Twenty four patients were tested for C reactive protein (latex agglutination test, normal <8 mg/l); rheumatoid factor (latex agglutination test, negative <1/20); and antinuclear antibody (indirect fluorescent antibody technique, negative <1/40). Plain radiography, isotopic scan of bone and joint, and electrocardiography were performed when indicated.

Patients were treated with oral trimethoprim sulphamethoxazole (co-trimoxazole) or tetracycline for at least six weeks in combination with intramuscular streptomycin for the first three weeks or oral rifampicin for a minimum of six weeks. In cases of osteomyelitis a combination of co-trimoxazole and rifampicin for 12 weeks together with streptomycin for the first three weeks was given. Tetracycline was only given to children older than 8. Patients were followed up fortnightly until the end of the treatment period, monthly for three months, and there-

after every three months. Relapse was judged by a recurrence of symptoms and signs of the disease, a positive blood culture, or a rising antibody titre after treatment, in the absence of re-exposure to infection.

Results

Duration of illness ranged from four to 150 days (mean 32·7). It was less than two weeks in 17 (43%) of the cases, two to 12 weeks in 20 (50%), and more than 12 weeks in three (8%). Table 1 shows the clinical manifestations in the 40 patients with osteoarticular brucellosis. All the 40 patients presented with true arthritis, which was manifested by pain, periarticular soft tissue swelling with or without obvious intra-articular effusion, limitation of motion, various degrees of hotness, and, rarely, by erythema. Table 2 shows the distribution of the joints affected in 40 patients with arthritis. Arthritis was monoarticular in 28 cases (70%) and pauciarticular in the remainder. No difference in the sex distribution of the patients with monoarthritis as opposed to pauciarthritis was seen. In preschool children monoarthritis represented 91% of joint disease compared with 62% in older ones, but the difference was not statistically significant. Of the 12 patients with pauciarthritis, two patients each had both hips, knees or sacroiliac joints affected respectively and six patients had three or four asymmetrical joints involved. Most patients with multiple joint disease tended to have an additive rather than a migratory arthritis. Spondylitis and arthritis of small joints of the hands and feet were not seen. Two female patients with arthritis of the hip had osteomyelitis of the adjacent proximal end of the femur; in one operative decompression, debridement and drainage of the hip joint was necessary.

Table 1 Clinical manifestations in the 40 children with osteoarticular brucellosis

Symptom/sign	*Number of patients (%)*
Fever	37 (93)
Arthralgia	36 (90)
Myalgia	24 (60)
Weight loss	20 (50)
Anorexia	18 (45)
Low backache	8 (20)
Sweating	6 (15)
Arthritis	40 (100)
Splenomegaly	10 (25)
Hepatomegaly	8 (20)
Lymphadenopathy	8 (20)
Osteomyelitis	2 (5)

Table 2 Distribution of joints affected and articular pattern in 40 patients with arthritis

Joints affected	*Pattern of arthritis*		*Total (%)**
	Monoarticular (n=28)	*Pauciarticular (n=12)*	
Hip	17	7	24 (41)
Knee	8	13	21 (36)
Ankle	2	3	5 (8)
Sacroiliac	—	5	5 (8)
Wrist	1	1	2 (3)
Elbow	—	1	1 (2)
Shoulder	—	1	1 (2)
Total number	28	31	59

*Shown as a percentage of the total number of joints affected.

Table 3 Initial laboratory findings in 40 patients with arthritis

Laboratory test	*Number of patients (%)*
Anaemia	16 (40)
Leucopenia	14 (35)
Lymphopenia	15 (38)
Neutropenia	13 (33)
ESR† (mm/h)	
20–40	11 (28)
>40	17 (43)
Positive C reactive protein	8 (33)*
Positive antinuclear antibody	6 (25)*
Positive rheumatoid factor	5 (21)*
Increased liver enzymes	16 (40)

*Percentage refers to 24 patients tested.
†ESR=erythrocyte sedimentation rate.

Thirty six of the 40 patients also had arthralgia in joints other than the joints affected by arthritis; the arthralgia manifested as intermittent or migratory pain of large or small joints, or both, with or without limitation of movements.

Table 3 presents the initial laboratory findings. Mild anaemia was present in 16 (40%) patients and correlated closely with the duration of illness. The peripheral blood picture did not show leucocytosis or relative lymphocytosis. The antistreptolysin O titre was normal in all 28 patients tested. Low titres of antinuclear antibody (range 1/40–1/80) were detected in six (25%) and rheumatoid factor (range 1/20–1/60) in five (21%) of 24 patients evaluated. Five of the six patients with positive antinuclear antibody test and all five patients with positive rheumatoid factor had positive brucella blood cultures. All 40 patients had significant brucella agglutination titres ranging from 1/160 to 1/20 480. The lowest titre was 1/160, found in three patients with positive blood cultures. *B melitensis* was isolated from the blood of 22 (71%) of 31 patients tested. All other biochemical tests and electrocardiograms were normal.

Synovial fluid was obtained from nine

Figure 1 A 6 year old girl with a five month history of right hip pain and limping. Radiograph of the pelvis shows advanced destruction and deformity of right femoral head and acetabulum.

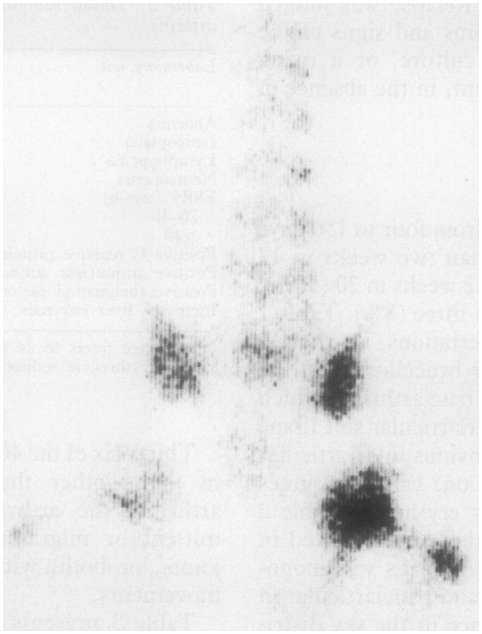

Figure 2 An 11 year old girl with right hip and back pains. Posterior scintigram discloses increased uptake in the right hip and sacroiliac joints.

patients. It varied from cloudy straw-colour to thick yellow. The mean leucocyte count was $14{\cdot}3\times10^9$/l (range $4{\cdot}2$–$32{\cdot}8\times10^9$/l) with variable polymorphonuclear or mononuclear predominance. The mean glucose content was 4·1 mmol/l (range 2·1–5·9 mmol/l) and the mean protein content 49 g/l (range 31–64 g/l). *B melitensis* was recovered from the synovial fluid culture in six patients, of whom one had a negative blood culture. Hence, brucella was detected in 23 (74%) of 31 patients by blood and synovial fluid cultures.

Plain radiographs, obtained in 14 patients, generally showed normal findings or merely confirmed periarticular soft tissue swelling or intra-articular effusion. In one patient only the plain radiograph showed severe articular destruction of the hip joint extending into the adjacent bones (fig 1). Technetium-99m bone scan was performed in eight patients with low backache as part of the initial evaluation of spinal involvement. There was no scintigraphic evidence of spondylitis in any of the eight patients, but increased uptake was noted in the hip and sacroiliac joints of four and two patients respectively (fig 2). Plain radiographs of the spine and pelvis were normal in all eight patients. Scintigraphic studies in four patients with clinically suspected osteomyelitis of the long bones disclosed increased radionuclide uptake in the upper femoral metaphysis of one patient, decreased uptake in the epiphysis and head of the femur of another patient, who also had radiographic evidence of severe hip joint destruction, and a normal scan in the remaining two patients.

All 40 patients were admitted to hospital for an average of 12 days (range 8–46). Initial clinical improvement occurred after an average of five days' treatment with antibiotics, and signs of arthritis resolved completely within one to two weeks later in all but one who had destructive hip arthritis and femoral osteomyelitis. Three patients were lost to follow up. There were three relapses among the remaining 37 patients, who have been followed up for an average of 12 months (range 9–36). All three relapses were treated successfully with another six week course of antibiotics. Only one patient still has considerable functional limitation of the hip joint and significant shortening of the affected limb as a result of severe destructive hip arthritis (fig 1).

Discussion

It is not well known that brucellosis due to *B melitensis* is quite common among children in areas where the disease is endemic.[19] A few case reports and a handful of series of cases of osteoarticular brucellosis in children have been described.[8 13 15 16 20] We found osteoarticular complications in 40 (38%) of 106 cases comparable with the incidence of 33·8% reported by Gotuzzo *et al*[14] and 37·4% observed by Mousa *et al*,[17] but both these studies considered only a small number of children.

As brucellosis is notoriously a multisystem disease with varied manifestations, epidemiological information is considered the key to diagnosis.[21] The infection in our cases was due to consumption of raw milk and contact with potentially infected animals. Absence of recognised exposure to contaminated animals and its products does not preclude the diagnosis, however, as three (8%) of our 40 patients had no such exposure.

In this study all patients but three had an acute onset with significant constitutional upset and a short duration—less than three months—of illness before presentation. One patient who had significant damage to the hip joint had the longest delayed presentation—five months. Although no significant difference in the sex distribution of brucellosis below the age of 14 has been observed by others,[19] female subjects showed preponderance over male subjects and school-age children over toddlers in osteoarticular complications in our series. Female predominance has been noted in two other small series of children with osteoarticular brucellosis[13 15] but has not been sufficiently emphasised. Further evidence of this tendency was reported by Gotuzzo *et al*, who noted that articular manifestations were more common in women than in men among 39 Peruvian families with brucellosis.[18] The role of age and sex in influencing the propensity to osteoarticular disease in brucellosis has yet to be clarified.

Peripheral arthritis has been described as the commonest form of osteoarticular complications in acute brucellosis.[15–18 22] This was the case in 37 (93%) of our 40 cases. Moreover, arthritis was monoarticular in two thirds of our cases and had a predilection for large weight-bearing joints. Monoarticular arthritis was more common among the younger than the older children. The vast majority of our patients with monoarticular or pauciarticular arthritis had hip and knee joints predominantly affected, as found by other workers.[13–17] Sacroiliitis, seen commonly in young adults,[14] occurred in only

three (8%) of our 40 patients; all were female and older than 10. Of special interest and particular significance is the absence of spinal and small joint disease among our cases in contrast with the findings in adults.[4–6 10 11 14 17] The results of this study show that brucellar arthritis usually runs a benign course and responds readily to antibiotic treatment. This is consistent with published reports.[4 14–17] It rarely progresses to osteoarticular destruction[8]; this occurred in only one of our cases.

It is currently believed that infectious and reactive arthritides occur in brucellosis,[14 23] as in other bacterial infections. In the present series the absence of initial migratory pattern and of recurrences of arthritis after treatment, the biochemical and bacteriological findings of synovial fluid, and the clearcut effect of antibiotic treatment on the course of arthritis all argue strongly against reactive arthritis. Our data, nevertheless, do not exclude the possible development of reactive arthritis in patients with brucellosis. Different osteoarticular patterns of the disease may be produced by the same or different brucella species depending upon the host's reaction, as with salmonella organisms.[24]

Osteomyelitis of the long bones, a rare complication of brucellosis,[9 12 16] was diagnosed in two female patients and was coexistent with destructive hip arthritis in one. Both patients were treated successfully with a combination of three antibiotics for 12 weeks.

Although haematological abnormalities were common accompaniments of brucellosis, the lack of a consistent pattern precluded their diagnostic value. Mild anaemia and leucopenia have been reported to occur frequently in patients with brucellosis.[3 13 25] These abnormalities were found in more than one third of our cases. In contrast with published reports emphasising the presence of the characteristic lymphocytosis,[16 26] our patients had normal leucocyte count or leucopenia with lymphopenia or neutropenia. The erythrocyte sedimentation rate and C reactive protein may or may not be raised and are only of prognostic significance if the level was previously raised.[10] The erythrocyte sedimentation rate and C reactive protein were raised in two thirds and one third of our patients respectively.

Immune abnormalities are reported in active brucellosis,[4 14 22] as in other infectious disorders.[27] The present findings of weakly positive titres of circulating antinuclear antibodies in six (25%) and rheumatoid factor in five (21%) of 24 patients tested compare well with an incidence of 25% and 37·5% respectively in a group of patients evaluated by Bocanegra *et al.*[22] It is noteworthy that these positive results were detected mostly in older children with positive brucella culture and with different articular patterns. The exact significance of these findings is not clear. The multisystem involvement in this infection is more suggestive of an immune complex process, however. Bocanegra *et al* showed the presence of circulating immune complexes in 91·5% of their patients with brucellosis.[22]

Although isolation of the causative organisms provides unequivocal evidence of brucellosis, the diagnosis is usually made by demonstrating a significant or rising brucella antibody titre. A 74% isolation rate of *B melitensis* in our series is comparable with the 77% reported by Norton[4] but is higher than that reported by others.[15–17] The findings in synovial fluid are similar to those seen in other forms of septic arthritis. Several investigators have assessed the value of synovial tissue and fluid findings in the diagnosis of brucellar arthritis.[4 12 14 17 20] Coventry *et al* noted that the isolation of brucella organisms increases significantly when synovial tissue rather than fluid is cultured as these organisms are intracellular inhabitants and are freed intermittently into body fluids.[28] Thus it is difficult to know whether arthritis is truly reactive or not when the aspirated synovial fluid is sterile, as it was shown to be in three of our nine cases. In our experience synovial fluid aspiration is rarely necessary for the diagnosis of acute brucellar arthritis. Joint decompression is mandatory, however, if a large tense effusion is accumulated where the blood supply to the joint may be compromised.

The value of radiographic and scintigraphic abnormalities in osteoarticular brucellosis has been assessed in detail by other investigators.[5 6 14] In this study we found that bone scintigraphy is more helpful than conventional radiography in localising a deep infection in the hip or the sacroiliac joint.

The efficacy of chemotherapy for any infection is largely judged by the rate of cure and the incidence of sequelae. The unpredictable relapse after treatment, however, has remained a significant problem in brucellosis as the organisms are facultative intracellular pathogens relatively inaccessible to antibiotics.[29] Furthermore, relapses are almost invariably associated with insufficient duration of treatment or failure of patients to take prescribed drugs.[30] The most outstanding result from this series of cases is the low relapse rate after treatment with two or three antibiotics combined for a minimum of six weeks. Similar results have been reported with one or two drugs given for short duration.[16]

In conclusion, the present series suggests that the incidence of brucellosis in children may be higher than is usually realised. The prevalence of osteoarticular complications in children seems to be similar to that in adults, but the pattern of bone and joint disease is different. Peripheral arthritis is the predominant form in children and is more commonly monoarticular with predilection for large weight-bearing joints. Age and sex seem to have an influence on the incidence and the expression of the osteoarticular manifestations of brucellosis in children. Diagnosis of brucellosis should be considered whenever there is a febrile illness associated with rheumatological complaints. Early recognition of the infection, prolonged antibiotic treatment, and careful long term follow up should improve the outcome of patients.

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