Brucellosis in children in south Jordan

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داء البروسيلات بين الأطفال في جنوب الأردن

عيسى صالح حجازي وجمال سعايطة

خلاصة: قمنا بإجراء تقييم استرجاعي لسجلات ثمانية وستين طفلاً مصابين بداء البروسيلات. فوجدنا أن 58.2% منهم سبق أن تناولوا ألباناً ومنتجات ألبان غير مبسترة. وشملت الظواهر غير النوعية التي عانوها، آلام المفاصل (78%) والحمى (75%) والتعرق (60%). أما الظواهر الموضعية فقد شملت العرج (75%) والتهاب المفاصل (54%). ووجد ابيضاض الدم لدى 51% من الأطفال، وفقر الدم في 24% منهم. وأمكن استنبات أنواع البروسيلات من دماء ستة عشر مريضاً (23.5%). وثبت أن التوافيق الدوائية المحتوية على الستربتوميسين كانت أكثر فاعلية من توافيق الجنتاميسين.

ABSTRACT Retrospectively we evaluated the records of 68 children with brucellosis. We found 58.2% had consumed unpasteurized milk and dairy products. Nonspecific manifestations included: arthralgia (78%), fever (75%) and sweating (60%). Localized manifestations included limping (75%) and arthritis (54%). Leukopenia was found in 51% of children and anaemia in 24%. *Brucella* species was cultured for blood of 16 (23.5%) patients. Combination therapy containing streptomycin was more effective than gentamicin combinations.

La brucellose chez les enfants dans le sud de la Jordanie

RESUME Nous avons procédé à une évaluation rétrospective des dossiers de 68 enfants atteints de brucellose. Il est apparu que 58,2% avaient consommé du lait et des produits laitiers non pasteurisés. Les manifestations non spécifiques comprenaient l'arthralgie (78%), la fièvre (75%) et la sudation (60%). Les manifestations focalisées comprenaient la claudication (75%) et l'arthrite (54%). Une leucopénie a été observée chez 51% des enfants et une anémie chez 24% d'entre eux. Des cultures de l'espèce Brucella ont été effectuées à partir du sang de 16 (23,5%) patients. Le traitement par association médicamenteuse contenant de la streptomycine était plus efficace que les associations médicamenteuses comportant de la gentamicine.

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Introduction

Brucellosis is a common zoonotic infection worldwide and is caused by the genus *Brucella*. Molecular genetic data indicate that the genus *Brucella* consists of species and biovars within a single species; but the definitive taxonomy of *Brucella* is still pending [*1*].

Four species are known to be transmissible to man: *B. suis*, *B. canis*, *B. abortus* and *B. melitensis*, the last being the most prevalent in the Mediterranean region [*2,3*]. The most virulent and invasive species usually affect goats and sheep and are transmissible to man through consumption of unpasteurized milk or dairy products from infected animals. Brucellosis occurs in all seasons, most commonly in spring and summer, and mostly in adult males. It may occasionally affect children but rarely before the age of 3 years. It may run an acute, subacute or chronic course depending on the immunological response of the patients themselves [*3,4*].

Lifelong immunity after infection does not occur, so the disease has a tendency to recur and become chronic [*5*]. Brucellosis is a multisystemic disease with a broad spectrum of clinical manifestations. It may present as fever of unknown origin and can remain undiagnosed for a long period of time [*6,7*]. Brucellosis tends to affect the musculoskeletal system and arthralgia and fever are the most common presentations.

Brucellosis is an endemic disease in Jordan as evidenced by a marked increase in the number of reported cases by the Jordanian Ministry of Health [*8,9*]. In the years 1988–1994, 4989 cases of brucellosis were reported, 1704 (34.2%) of which were in children under 14 years [*9,10*]. This increase could be attributed to an increased awareness and reporting the disease, the importation of infected cattle and sheep and the availability of unpasteurized milk.

Materials and methods

Records of the preceding 3 years of 68 children with brucellosis from 3 hospitals were studied retrospectively. Ages ranged from 3 years to 14 years. All met the standard and case definition of this descriptive study. Criteria for case inclusion included a compatible clinical picture with either a positive blood culture for *Brucella* organism or a *Brucella* antibody titre ≥ 1:160 and/or rising titre. Cases not fulfilling the abovementioned criteria were excluded. Relapse was defined as recurrence of symptoms within 6 months of the initial diagnosis with persistent high titre and/or rising titre. Cure was defined as no recurrence of symptoms within 6 months of the initial diagnosis.

Initial laboratory investigations included complete blood cell count and the agglutination test using rose Bengal plate, which has the capability to detect antibodies of IgM and IgG classes against three *Brucella* species (*B. melitensis*, *B. abortus* and *B. suis*). *Brucella* spp. titre was measured using Wright's test with proper dilution of sera to avoid the prozone phenomenon. Diphasis blood culture medium (Hemoline, bioMérieux, France) was incubated for at least 4 weeks. Bone marrow aspirate culture and bone marrow trephine biopsy are not available for use in the diagnosis of brucellosis in south Jordan.

The following eight combinations of antimicrobial treatment were administered in paediatric doses.

- Streptomycin injection for 2 weeks plus tetracycline orally for 6 weeks;
- Co-trimoxazole orally for 6 weeks plus rifampicin orally for 6 weeks:

- Co-trimoxazole orally for 6 weeks plus gentamicin injection for 5 days;
- Co-trimoxazole orally for 6 weeks plus streptomycin injection for 2 weeks;
- Streptomycin injection for 2 weeks plus rifampicin orally for 6 weeks;
- Tetracycline orally for 6 weeks plus co-trimoxazole orally for 6 weeks;
- Tetracycline orally for 6 weeks plus gentamicin injection for 5 days;
- Rifampicin orally for 6 weeks plus gentamicin injection for 5 days.

Tetracycline was not used for children under 8 years.

Results

Records of 68 children were reviewed; 40 males (58.8%) and 28 females (41.2%). Ingestion of unpasteurized milk was reported in 40 children (58.8%), animal contact in 19 (27.9%), while 26 children (38.2%) appeared to have no history of exposure to either. Also, 31 patients (45.6%) had a positive family history of brucellosis.

The most common clinical manifestations were: arthralgia in 53 (78%) children, fever in 51 (75%), limping in 51 (75%), night sweats in 41 (60%), arthritis in 38 (56%), splenomegaly in 23 (34%) and hepatomegaly in 17 (25%). Other less common manifestations such as anorexia, weight loss, abdominal pain and lymphadenopathy were not included in our study. Haematological findings were leukopenia in 37 children (54%) followed by anaemia in 16 (24%), thrombocytopenia in 7 (10%) and pancytopenia in 4 children (6%). A total of 23 (34%) children had normal blood counts. Table 1 shows that 62 patients (91.2%) had antibody titres < 1:640, while only 12 of these had positive blood cultures. In contrast, the other 6 patients (8.8%) with higher titres had 4 positive blood cultures. Table 2 shows that the presence of more frequent clinical manifestations was directly proportional to higher titres. The only patient who had a titre of 1:2560 had all the clinical manifestations except night sweating.

Table 3 demonstrates the correlation between different titres and haematological findings. Leukopenia was found in 37 patients and but was not correlated with high titres, while anaemia which was found in 16 patients, thrombocytopenia in 7 patients and pancytopenia in only 4 patients were correlated with high titres.

All patients showed a clinical response within 2 weeks of initiation of antimicrobial therapy, but 22 (32.4%) subsequently relapsed. Of the 17 patients who received gentamicin in combination, 5 (29.4%) were cured and 12 (70.6%) relapsed. Of the 36 (52.9%) patients who received streptomycin in combination, only 4 (11.1%) patients relapsed and the cure rate ranged from 80% to 100%. Other regimens not containing streptomycin or gentamicin had relapse rates varying from 20% to 40%. Cure and relapse rates with both drugs were not related to the *Brucella* titre. These findings are shown in Tables 4 and 5.

Table 1 **Number of cases of different antibody titres and correlation between titre and positive blood culture**

Titre	No. of patients (n = 68)	%	No. of patients with positive blood culture	%
1/160	13	19.1	1	7.7
1/320	33	48.5	7	21.2
1/640	16	23.5	4	25.0
1/1280	5	7.4	3	60.0
1/2560	1	1.5	1	100.0

Table 2 Correlation between different antibody titres and frequency of clinical manifestations

Titre	Clinical manifestation													
	Arthralgia		Fever		Limping		Night sweats		Arthritis		Splenomegaly		Hepatomegaly	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1/160 (n = 13)	9	70	8	62	8	62	6	46	8	62	2	15	2	15
1/320 (n = 33)	26	79	24	73	25	76	19	58	16	48	9	27	6	18
1/640 (n = 16)	13	81	13	81	13	81	10	63	10	63	8	50	6	38
1/1280 (n = 5)	4	80	5	100	4	80	5	100	3	60	3	60	2	40
1/2560 (n = 1)	1	100	1	100	1	100	0	0	1	100	1	100	1	100

Discussion

Although 26 patients in our study appeared to have no history of exposure to risk factors (milk ingestion, animal contact and positive family history), we believe that these patients must have had some sort of exposure. Milk and dairy products appear to have an associated relationship with brucellosis with a relative risk of 1.54. However, animal contact did not appear to have the same effect (relative risk 0.73). A study of the epidemiology of human brucellosis in California by Chomel et al. showed that between 1973 and 1992, human brucellosis in California evolved from an occupational to a foodborne illness [*10*].

Arthralgia was the most common presenting symptom followed by fever, as in many other studies [*11*]. Arthralgia was found in 61% of patients and occurred more often in children than in adults (74% versus 52%) ($P < 0.05$) in a study conducted in Israel [*12*]. In a prospective study in Jordan, fever (88%) was the most common clinical feature encountered, followed by sweating, arthralgia and general weakness [*13*], while in a study in Saudi Arabia, fever was present in 100% of patients and arthralgia in 25% [*14*].

Our results showed that patients who had higher titres also had more severe disease. This is clear by the more frequent appearance of more symptoms and signs in patients with higher titres. Haematological disturbances in bruellosis are common, in particular leukopenia. The frequencies of haematological findings in Benjamin's study were leukopenia (38%), anaemia (64%) and thrombocytopenia in (28%) [*14*]. Another study of haematological changes during the active course of brucellosis showed that

Table 3 **Correlation between different antibody titres and haematological findings**

Titre	Leukopenia		Anaemia		Thrombocytopenia		Pancytopenia	
	No.	%	No.	%	No.	%	No.	%
1/160 (n = 13)	11	85	0	0	0	0	0	0
1/320 (n = 33)	8	24	3	9	1	3	0	0
1/640 (n = 16)	14	88	8	50	2	13	2	13
1/1280 (n = 5)	3	60	4	80	3	60	1	20
1/2650 (n = 1)	1	100	1	100	1	100	1	100

Table 4 **Different drug combinations and their cure and relapse rates**

Combination	Total no.	%	No. cured	No. relapsed	Relapse rate (%)
Streptomycin + tetracycline	24	35.3	21	3	12.5
Streptomycin + co-trimoxazole	7	10.3	7	0	0
Streptomycin + rifampicin	5	7.4	4	1	20.0
Gentamicin + co-trimoxazole	9	13.2	4	5	55.6
Gentamicin + tetracycline	5	7.4	1	4	80.0
Gentamicin + rifampicin	3	4.4	0	3	100.0
Co-trimoxazole + rifampicin	10	14.7	8	2	20.0
Tetracycline + co-trimoxazole	5	7.4	1	4	80
Total	68	100	46	20	29.4

leukopenia occurred in 33% of patients, anaemia in 44%, thrombocytopenia in 5% and pancytopenia in 14% [6]. Our results showed a correlation of anaemia, thrombocytopenia and pancytopenia with high titres ($P < 0.05$) but not for leukopenia.

There is a strong association of high antibody titre with positive blood culture and

Table 5 **Cure and relapse rates in patients with different titres treated with gentamicin in combination versus patients treated with streptomycin in combination**

Titre	Gentamicin +			Streptomycin +		
	Total no.	No. cured	No. relapsed	Total no.	No.cured	No. relapse
1/160	3	1	2	16	15	1
1/320	5	1	4	11	10	1
1/640	6	1	5	6	4	2
1/1280	3	2	1	2	2	0
1/2560	0	0	0	1	1	0
Total	17	5	12	36	32	4

this suggests that initial high titre is a predictor for blood culture positivity and arguably for a more serious *Brucella* infection [*14*].

Treatment of childhood brucellosis is controversial and is currently dependent on the inclusion of an aminoglycosidic antibiotic. It is evident from other research that therapy with a single antibiotic is not as effective in brucellosis as when appropriate combinations are used [*15*]. Our study showed that gentamicin in combination had much less satisfactory results than streptomycin in combination ($P < 0.01$). However, Lubani et al. in Kuwait demonstrated that gentamicin in combination had satisfactory results in treatment of brucellosis [*16*]. A multicentre prospective study carried out by Cisneros et al. on antimicrobial therapy for brucellosis concluded that the combination of doxycycline and streptomycin was an effective treatment for the types of brucellosis included in their study [*17*]. Solera found that the combination of doxycycline (45 days) and rifampicin (21 days) was less effective than the classical combination of doxycycline and streptomycin [*18*]. In our study, other combinations excluding gentamicin and streptomycin (co-trimoxazole and rifampicin, tetracycline and co-trimoxazole) had better results than gentamicin in combination which supports the recommendation of Solera that the combination of rifampicin and co-trimoxazole as the preferred regimen for children < 8 years [*19*]. A study by Khuri Bulos et al. concluded that the combination of trimethoprim–sulfa methoxazole and rifampicin was both cost-effective and safe for the treatment of childhood brucellosis [*20*]. The failure of gentamicin in our study could be attributed to the fact that streptomycin was used for 2 weeks but gentamicin was used for only 5 days. Bertrand raised the point that adequate duration of therapy was as important as selecting the appropriate combination [*21*]. Solera et al. found that the relapse rate obtained with doxycycline treatment for 30 days was higher than that obtained with doxycycline treatment for 45 days [*22*].

Conclusions

- Ingestion of unpasteurized milk or dairy products was the most common source of *Brucella* infection; therefore milk should not be drunk unless pasteurized

and careful history should always be obtained.

- Arthralgia and fever were the most common presenting symptoms.
- Brucellosis should always be considered in any child presenting with fever and nonspecific musculoskeletal complaints.
- Haematological findings associated with severe disease included anaemia, thrombocytopenia and pancytopenia but not leukopenia.
- *Brucella* agglutination test and titre in association with a suggestive clinical picture was more sensitive than blood culture in the diagnosis of brucellosis. Indeed significantly high titres correlated with severity of the disease, frequency of haematological findings and positivity of blood culture.
- Prescriptions must be long enough not only to achieve cure but also to eliminate the *Brucella* strain and avoid relapse.
- The findings of our research are in agreement with other studies that suggest streptomycin in combination is superior to gentamicin in combination.
- Cure and relapse with any combination was not dependent on antibody titre.

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Note from the Editor

The next issue of the EMHJ, Vol 5 No. 6 of November 1999, will be a special issue on human genetics. It will be the last issue under Volume 5(1999).