Research Article

Brucellosis in Southern Israel: Comparison between Children with and without Hematological Manifestations

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Abstract

Objectives: We characterized the epidemiological, diagnostic and clinical aspects of children <18 years presenting with brucellosis accompanied by hematologic manifestations in Southern Israel.

Method and Patients: A retrospective study on children hospitalized with brucellosis and diagnosed clinically, as well as by positive blood cultures. Patients with hematologic involvement were compared with patients w/o hematologic involvement.

Results: 128/252 (50.8%) children were diagnosed with brucellosis and had blood cultures positive for *Brucella melitensis*. Thirty-three (25.8%) had hematologic manifestations (leukopenia 32, thrombocytopenia 14, 13 both). In univariate analysis, more males were diagnosed with hematologic involvement while no differences were seen between the 2 groups in known risk factors for brucellosis like use of non-pasteurized milk, contact with livestock, brucellosis among family members, clinical signs/ symptoms and presence of negative serological tests. The most common presentations in patients with hematologic manifestations were

monoarthritis, lymphadenopathy and hepatomegaly (36.7%, 17.2% and 12.5%, respectively) w/o any differences compared with patients w/o hematologic manifestations. Impaired liver function tests and recurrent disease were more frequent in patients w/o hematologic involvement *vs.* patients with hematologic involvement (42.5% *vs.* 9.2%, P=0.005 and 10.4% *vs.* 0%, P=0.06). High antibodies titers (1:640-1:1280) were more common in patients w/o hematologic involvement (28.4% *vs.* 6%, P=0.002). In 3 different multivariate statistical models, patients with hematologic manifestations were older than those w/o hematologic manifestations.

Conclusions: Brucellosis accompanied by hematologic manifestations is common in children in Southern Israel. Patients with hematological involvement did not present with major different characteristics compared with patients w/o hematological involvement. We recommend testing for brucellosis in all Bedouin children with leukopenia and/or thrombocytopenia in Southern Israel.

Keywords: Brucella; children; leukopenia; thrombocytopenia; pancytopenia

Introduction

Brucellosis is a multisystemic zoonotic infection diagnosed frequently in underdeveloped countries and in the rural areas of the developed world [1-5]. The most commonly isolated organism is *Brucella melitensis*, found primarily in goats, sheep and camels. Humans are usually infected through ingestion of raw milk, cheese, direct contact with infected animals, products of conception or animal discharges and inhalation of infected aerosols. The disease is characterized by a wide variety of symptoms and includes a considerable amount of nonspecific hematologic abnormalities, including anemia, leukopenia, thrombocytopenia and also pancytopenia [3, 4]. Infrequently, cases of disseminated intravascular coagulation, thrombotic thrombocytopenic purpura and hematophagocytic syndrome have been described [4, 6, 7]. Hypersplenism, haemophagocytosis and granulomatous lesions of the bone marrow appear to play a fundamental role in producing these abnormalities seen in the peripheral blood [6, 7].

In the Negev region of Southern Israel two populations of children live side by side: Jewish children, largely urban with lifestyle comparable to a Western population and Bedouin children formerly composed of desert nomads and now in transition to a Western lifestyle. Children belonging to the two populations differ in disease patterns and rates but both have access to the same medical services. The 2 pediatric populations also differ in disease patterns and rates. Hospitalizations rates due to respiratory and gastrointestinal infections in general, and due to invasive pneumococcal diseases particularly are more prevalent among Bedouin children [8-10].

In a prospective study conducted throughout 1998 to determine the frequency of selected bacterial zoonoses as causes of fever among hospitalized Bedouins in Southern Israel, one or more zoonoses were diagnosed in 30 (27%) of 110 patients admitted with fever. Brucellosis was diagnosed in 9 (8%) and rickettsial infections in 20 (18%) [11]. In a recent retrospective study on the epidemiologic, diagnostic and clinical characteristics of brucellosis in children in Southern Israel, Fruchtman *et al* reported on 128 patients < 19 years hospitalized during 2005-2011 [12]. All children had *B. melitensis* identified in

blood cultures and all were Bedouin Muslims (representative of a population characterized by a high incidence of Brucellosis, 16 cases/100,000 population during 2005-2012). The most common symptoms described were arthralgia, weakness and gastrointestinal complaints, while the most frequently reported findings in the physical examination were arthritis, hepatosplenomegaly and lymphadenopathy [12].

The purpose of the present study was to study the epidemiological, diagnostic, clinical and therapeutical aspects of children with *Brucella* bacteremia associated with hematologic manifestations in children in Southern Israel during 2005-2011. We determined the clinical picture of patients with *Brucella* bacteremia associated with hematologic manifestations and compared it with those w/o hematologic manifestations.

Patients and Methods

The Soroka University Medical Center (SUMC) is the only general hospital in Southern Israel and all the children in the region are born and treated there. It serves a population of >900,000 inhabitants (of them >250,000 children <18 years of age). Medical insurance in Israel for children is universal and is provided free of charge. There are no financial or other barriers for health-care service use in the region. Approximately 60% of Jewish children and 85%–90% of Bedouin children in the Negev are insured in the largest HMO in Israel, the Clalit General Health Insurance Plant. Overall treatment policies are identical in the 2 populations since drug formulations, prices, and availability of drugs is the same at all General Health Insurance Plan clinics. Criteria for referral to a hospital are also similar.

Study Population

The study population included all patients <19 years of age admitted at the pediatric departments, or examined, diagnosed and discharged from the Pediatric Emergency Room (PER) of SUMC between January 2005 through December 2012, with a diagnosis of brucellosis.

The study protocol was approved by the institutional ethical committee.

Diagnosis

The diagnosis was established according to a clinical presentation compatible with brucellosis + a positive blood culture. The serologic tests relied on agglutination tests (the Rose Bengal test and the serum agglutination test). A Standard Tube Agglutination Test (SAT) titers above 1:160, in conjunction with a compatible clinical presentation, was considered compatible with the diagnosis of brucellosis, but needed confirmation by a positive blood culture in order to have a definitive diagnosis of brucellosis. In the current study, in the absence of a positive blood culture, the serum agglutination test was considered an insufficient tool in the diagnosis of acute brucellosis.

Diagnostic blood cultures are obtained at the SUMC for inpatients and for individuals referred to the emergency departments only and no blood cultures are performed in the outpatient setting. It is estimated that SUMC provides diagnostic serologic testing for brucellosis to 90% of the relevant Bedouin population.

Blood cultures were obtained at the emergency department and inpatients' wards of the hospital using the Bactec 9240 system (Becton Dickinson).

Inoculated blood culture vials were incubated following the manufacturer's recommendations and negative vials were discarded after 7 days without further processing [13-16]. Brucellae were identified on the basis of a typical biochemical profile and positive agglutination reaction with specific antiserum (Welcome Diagnostics). Speciation was performed at the Kimron Veterinary Institute at Bet Dagan, Israel, with phages Tb and Iz.

Sera were screened for *Brucella* antibodies by the Rose-Bengal test [16]. Positive specimens were serially diluted from 1:20 up to 1:1280 to eliminate the ''prozone effect'' and tested by the standard agglutination test (SAT). A SAT titer of 1:160 was considered diagnostic of the disease.

Recurrence was defined by re-emergence of clinical signs and/or serologic evidence of new disease and/or positive blood cultures for *Brucella* following a one-month period after completion of therapy for the initial episode.

Clinical and laboratory data collection

The medical records of all patients admitted to the pediatric departments or discharged from the PER of SUMC during 2005-2012 with the diagnosis of *Brucella* bacteremia were searched and all the relevant demographic, microbiologic, clinical and therapeutic parameters were summarized, including:

- demographic and epidemiologic data (age, ethnicity, gender), contact with livestock, consumption of unpasteurized milk products
- background clinical conditions
- microbiologic data (blood cultures, cultures from localized sites of infection)
- clinical presentation leading to admission to hospital/PER
- complications of brucellosis at admission at PER or during hospitalization
- laboratory data at admission (CBC, liver function tests, electrolytes, renal function tests and *Brucella* serology)
- treatment data and length of hospitalization
- outcome data (recurrences recorded only in hospitalized patients)

Treatment

All patients diagnosed with brucellosis were treated according to one of the following protocols: 1) Children >8 years of age: PO doxycycline 2 mg/kg twice daily for six weeks + intravenous/intramuscular gentamicin 5 mg/kg/day for two weeks; 2) Children <8 years of age: PO sulfamethoxazole 20 mg/kg + trimethoprim 4 mg/kg twice daily for six weeks + intravenous/ intramuscular gentamicin 5 mg/kg/day) for two weeks. Information on the follow-up of the patients was not available.

Statistical analysis

Data were summarized using frequency tables for categorical variables and summary statistics (mean with standard deviation) for continuous variables.

T-test and ANOVA were used for comparing continuous variables and the chi-square test was used for categorical data, augmented by Fisher's exact test if needed. We used Mann-Whitney and Kruskal-Wallis test for the comparison of variables not distributed normally. All reported P values were two-sided and the level of $p< 0.05$ was considered statistically significant. Data analysis was performed using SPSS version 23 (SPSS Inc. Chicago, Illinois).

For multivariate analysis, we used a few different regression models, changing the independent variable

within them (patient age and gender, temperature, fever >39 ^{o}C, length of disease and of hospitalization, use of unpasteurized dairy products, contact with livestock and presence of relatives with brucellosis).

Results

Overall, positive blood cultures were recorded in 128/252 (50.8%) of the 252 children diagnosed with brucellosis during the study period, with *B. melitensis* isolated in all of them. These patients represent the study population. All 128 patients were of Bedouin Muslim ethnicity. Of them, 33 (25.8%) presented with hematologic abnormalities: 32 (25%) with leukopenia (<5000 WBC/ml), 15 (11.7%) with neutropenia, 14 (10.9%) with thrombocytopenia (<150,000/ml) and 13 (10.2%) with leukopenia and thrombocytopenia together. There was 1 (0.8%) patient with neutropenia <500 WBC/ml and 6 (4.7%) with neutropenia <1000 WBC/ml. Pancytopenia was seen in 3 (2.3%) patients. No differences were recorded between patients with hematological involvement and patients w/o hematological involvement in respect to contact with livestock and presence of brucellosis among relatives (Table 1). Overall, there were 82 (64 %) females and 46 (36%) male patients. More male patients were seen in the group of patients with hematologic manifestations (P=0.0005). No differences were seen between the 2 groups in the percentages of young patients <4 years of age. More patients aged 5-14 years belonged to the group of patients w/o hematologic manifestations while more patients aged 15-19 years belonged to the group of patients with hematologic manifestations. The patient history revealed that more patients in the group w/o hematologic manifestation reported on consumption of unpasteurized milk and presented with recurrent disease (P=0.06).

Table 1: Epidemiologic data: comparison between patients with hematologic manifestations and patients w/o hematologic manifestations.

Variables	All patients N=128	Patients with hematologic manifestations N=33	Patients w/o hematologic manifestations N=95	P value
Age years (Mean±SD)	8.48±4.81	8.6±5	4±4.86.	
0-4				
5-14	27	8 (24%)	19 (20%)	0.61 *
15-19	72	12 (36%)	60 (63%)	0.002
	29	13 (39%)	16 (17%)	0.008
Gender Male (n %)	46 (36%)	25 (75%)	21 (22.1%)	0.0005 **
Consumption of unpasteurized milk (n,%)	72 (56.2%)	14 (41%)	58 (61.0%)	0.06**
Contact to livestock (n, %)	86 (67.2%)	20 (59%)	66 (69.5%)	0.3 **
Brucellosis in relatives (n, %)	50 (39%)	15 (44%)	35(36.8%)	0.38 **
Recurrence (n, %)	10 (7.8%)	0	10 (10.4)	0.06 **

* Independent samples t-test; ** Pearson's Chi square

Overall, 32 (25%) patients with *Brucella* bacteremia suffered from pre-existing cardiovascular, respiratory, gastrointestinal, infectious, rheumatologic, immunologic or neurologic conditions/ pathologies, which were present in 14/33 (42 %) and 18/95 (18.9%) patients with hematologic manifestations and w/o hematologic manifestations, respectively (P=0.007). No significant differences were recorded between the 2 groups in respect to cardiovascular, respiratory, gastrointestinal, infectious, rheumatologic, immunologic or neurologic background conditions. Most patients (81.3%) were afebrile at admission, with no difference between the patients with hematologic manifestations and those w/o hematologic manifestations (Table 2). No differences were seen between the 2 groups in respect to complaints of arthralgia, weakness, myalgia, gastrointestinal symptoms, back pain, night sweating and weight loss. More patients w/o hematologic manifestations suffered from headache in the period of time preceding hospitalization (P=0.04). Overall, the most common clinical findings were monoarthritis, lymphadenopathy and hepatomegaly (36.7%, 17.2% and 12. 5%, respectively)**.** No significant differences were recorded in all clinical parameters studied between patients with hematologic manifestations and those w/o hematologic manifestations.

Table 2: Clinical features: comparison between patients with hematologic manifestations and patients w/o hematologic manifestations

Variables	**All patients n=128**	**Patients with hematologic manifestations n=33**	**Patients w/o hematologic manifestations n=95**	**P value**
Fever (Celsius) (Mean ±SD)	37.3 ± 0.9	37.14 ± 0.8	37.4 ± 0.85	
<38^{0}C (n, %)	100 (81.3)	28 (87)	72 (75.8)	0.14 **
38.1-39^{0}C (n, %)	17 (13.8)	(9)3	14 (14.8)	1.0
>39^{0}C (n, %)	6 (4.9)	2 (6)	4 (4.3)	0.33
Duration of symptoms (days) (Mean ±SD)	10.1 ± 10.9	11.67 ± 13	10.5 ± 12.1	0.26 *
< 7 days (n, %)	73 (59.8)	18 (54)	55 (60)	0.59
7-30 days (n, %)	46 (37.7)	12 (36.3)	34 (35.8)	0.26
> 30 days (n, %)	3 (2.5)	2 (6)	1 (1)	0.05
Arthralgia (n, %)	79 (61.7)	20 (60)	59 (62)	0.88**
Weakness (n, %)	42 (32.8)	15 (42)	27 (28)	0.14 **
Gastrointestinal symptoms (n, %)	35 (27.3)	7 (18)	28 (30)	0.21**
Myalgia (n, %)	32 (25)	8 (21)	24 (25)	0.64**
Headache (n, %)	24 (18.8)	9 (27)	15 (16)	0.04**
Back pain (n, %)	21 (16.4)	5 (15)	16 (17)	0.8**
Night sweats (n, %)	17 (13.3)	3 (9)	14 (15)	0.56**
Weight loss (n, %)	14 (10.9)	6 (15)	8 (8.3)	0.32**

***** Independent samples t-test; ** Pearson's Chi square

Table 3: Laboratory findings: comparison between patients with hematologic manifestations and patients w/o hematologic manifestations.

Variables (at admission)	All patients n=128	Patients with hematologic manifestations n=33	Patients w/o hematologic manifestations n=95	P value
Sodium (mEq/L) (Mean ±SD)	135.8 ± 2.8	136±2.59	135.7±2.9	0.601 *
Potassium (mEq/L) (Mean ±SD)	4.3 ± 0.4	4.2±0.5	4.31±0.39	0.198 *
Urea (mg/dL) (Mean ±SD)	22.7 ± 7.6	21.2±7.3	23.4±7.6	0.57 *
Urea >40 (mg/dL) (n, %)	3 (2.6)	0	3	0.99 **
ALT (IU/L) (Mean ±SD)	42.5 ± 58.2	30±27	44.5±55	0.005 *
ALT >40 IU/L (n, %)	43 (30.3)	3	40	<0.001 **
AST (IU/L) (Mean ±SD)	59.6 ± 56.5	43.7±38.3	59.54±51	0.46 *
AST>40 IU/L (n, %)	88(68.9)	21(63.6)	67(70)	0.47 **
C reactive protein* (mg/L) (Mean ±SD)	3.0± 3.1	1.82±1.7	2.53±2.72	0.08 *
C reactive protein >3 mg/L (n, %)	11 (35.5)	3(9)	8(8.4)	0.5 **
C reactive protein >5 mg/L (n, %)	6 (19.4)	2(6)	4(4.2)	0.65 **

* Independent samples t-test; ** Pearson's Chi square

The standard agglutination test for Brucella was negative in 9% and 10.5% patients with hematologic manifestations and patients w/o hematologic manifestations, respectively (Table 4). More patients w/o hematologic manifestations had agglutination tests between 1:640 - 1:1280 (P<0.002). There were no significant differences in the treatment regimens received by the 2 patient groups.

Statistical models: Regression multivariate analysis

The regression analysis included 117 patients (missing of 11 patients, 8.6% due to incomplete data). We used a few different regression models, changing the independent variable. All models had the presence of hematological manifestations as the dependent variable. In the model presented in Table 5, the total model significance was 0.003, with a -2 log likelihood of 62.53 and a Nagelkerke R square of 0.336, with an insignificant Hosmer and Lemeshow test (0.542). In all the models, age was a significant risk factor for hematological manifestations.

Discussion

In the present study, of the 128 patients with Brucella bacteremia included in the study, anemia, leukopenia, thrombocytopenia and pancytopenia were found in a considerable amount of patients (17.6%, 29.6%, 12.8% and 2.35%, respectively). We tried to determine in this study the characteristics of children with Brucellosis presenting with hematologic manifestations and compare these patients with the group of children diagnosed with Brucellosis w/o hematologic manifestations. We compared the disease history, clinical presentation, physical examination findings, inflammatory markers and

serological findings (serum antibody titers to *Brucella*) and tried to determine a practical management approach to the patients presenting with neutropenia and/or thrombocytopenia in our area, characterized by a high incidence of Brucellosis.

We found in this study that: 1. In multivariate analysis including epidemiological and clinical parameters, the patients with brucellosis and hematologic manifestations were older than those w/o hematologic manifestations; 2. The disease history, reports of contact with livestock, presence of brucellosis among relatives, clinical presentation, physical examination findings and laboratory examinations did not differ between the 2 patient groups; 3. The serologic findings (anti Brucella antibody titers) were not different between the two study groups groups.

Brucellosis associated with hematologic manifestations was described in children in a limited number of studies. Al-Eissa *et al*[7] described in 1993 in Saudi Arabia 111 children diagnosed with brucellosis and reported anemia, leukopenia, thrombocytopenia and pancytopenia in 44%, 33%, 5% and 14% of the patients. In Turkey, Karakuku *et al*[17] described 8 (14.8%) patients with pancytopenia among 56 children diagnosed with brucellosis during 1996-2003. The authors reported that all 8 patients had Brucella agglutination titers of at least 1:320, the titers did not correlate with the degree of pancytopenia, most patients had hepatosplenomegaly and bone marrow aspiration specimens showed hypercellularity or normal cellularity.

Since 2010, 6 studies (including the present study) addressed the issue of hematologic abnormalities among children with brucellosis (Table 6) [6, 18-21]. These studies enrolled 1654 children with brucellosis and reported hematologic manifestations in 9.6%-46.9% of the patients. Specifically, anemia, leukopenia, thrombocytopenia and pancytopenia were found in 13.3-96.0%, 10.2-68.0%, 3.4-100% and 1.8-8.3% of the patients. Positive blood cultures for *Brucella* spp. were reported in 1.9-100% of the patients and bone marrow aspirations (performed only in patients with pancytopenia and reported in only 4 studies) in 73 (9.0%) of the 815 patients enrolled in these studies. The common bone marrow aspiration findings consisted in hyperplasia of the erythroid series, a shift to the left of the granulocytic series, megakaryocytosis, hystiocytic hyperplasia and mild hemophagocytosis [18, 20]. Interestingly, seronegativity was found in a relatively high rate (13.7%) among the patients enrolled in our study, finding absent in the other 5 studies. In the majority of patients the pancytopenia regressed completely and the peripheral blood counts returned to normal after treatment of *Brucella* infection. *Brucella*-induced immune thrombocytopenic purpura was symptomatic in the majority of patients, presented with severe thrombocytopenia and required intravenous gamma globulin therapy [17]. Yustman *et al.* [21] reported, in univariate analysis, that older age, presence of fever at diagnosis, positive blood cultures and IgM ≥1:640 levels were associated with cytopenia. However, in multivariate analysis, only older age and fever were associated with cytopenia.

As with any study, ours is not devoid of limitations. The retrospective nature of the study prevented us from making inferences about causality, and all our results are essentially an association. In addition, the enrollment of only hospitalized patients and lack of follow-up and compliance information may limit the generalization of our data.

In conclusion, we found that Brucellosis accompanied by hematologic manifestations is common in southern Israel, but the patients with

hematologic involvement did not present with major different characteristics compared with those w/o hematologic involvement, neither in symptomatology and laboratory findings nor in management of this condition. We recommend testing for brucellosis in all Bedouin children presenting with leukopenia and/or thrombocytopenia in southern Israel.

Potential Conflicts of Interest

The authors have no conflicts of interest relevant to this article to disclose

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Table 4: Brucella agglutination titers: comparison between patients with hematologic manifestations and patients w/o hematologic manifestations^

Brucella **titers**	**All patients with positive *Brucella* culture n=95**	**Patients with hematologic manifestations n=21**	**Patients w/o hematologic manifestations n=74**	**P value**
>1:1280	14 (14.7)	5 (15)	9 (9.4)	0.3**
1:640-1:1280	29 (30.5)	2 (6)	27 (28.4)	0.002**
1:320-1:640	22 (23.2)	7 (21)	15 (15.8)	0.25**
1:160-1:320	16 (16.8)	4 (12)	12 (12.6)	0.75 **
<1:160	13 (13.7)	3 (9)	10 (10.5)	0.99**

^ serum agglutination titers determined in 95 of the 128 patients with positive blood cultures

* Independent samples t-test; ** Pearson's Chi square

Table 5: Multivariate analysis: comparison between patients with hematologic manifestations and patients w/o hematologic manifestations according to various epidemiologic and clinical factors

		Exp(B)	**df**	**Sig.**
	Gender	1.196	1	0.794
	Age (years)	1.292	1	0.002
	Body temperature	0.541	1	0.115
	Use of unpasteurized dairy products	0.434	1	0.252
	Length of hospital stay	1.047	1	0.694
	Constant	318335019.2	1	0.177

Table 6: Literature review: medical studies completed during 2010-2019 and analyzing the hematologic manifestations of brucellosis in children

Reference No.	Country (study period)	No. patients enrolled	Age (years)	Hematologic abnormalities (%)	Anemia (%)*	Leukopenia (%)*	Thrombocytopenia (%)*	Pancytopenia (%)*	Blood Cx. (+) for Brucella (%)*	Bone marrow aspiration / biopsy (%)*	Agglutination titers
6	Turkey (2004-2009)	146	<16	14 (9.6)	9/14 (64.3)	29 (19.7)	5 (3.4)	9 (6.2)	8/9 (88.9)	14/14 (100)	1:320 (6) 1:640 (2) 1:12809 (1)
18	Turkey (2004-2010)	187	<16	25 (13.3)	24/25 (96.0)	17/25 (68.0)	25 (100.0)	17 ((9.1)	3/25 (12.0)	2/25 (8.0)	1:320 (1, 4%) 1:1280 (24, 96.0%)
19	Saudi Arabia (2011-2012)	60	Mean 7.6 (5-16)	NM	26 (43.3)	23 (38.3)	NM	11 (8.3)	23 (38.3)	9/60 (15.0)	1:160-1:320 (3, 5%) >1:320 (8, 13.3%)
20	Turkey (2009-2015)	622	Mean 11 (1-16)	292 (46.9)	178 (28.6)	87 (13.9)	100 (16.1)	48 (7.7)	12 (1.9)	48 (7.7)	>1:160 all patients
21	Israel (2005-20140	511	Mean 9.8	214 (41.9)	68 (13.3)	144 (28.2)	74 (14.5)	9 (1.8)	364/463 (78.6)	NM	IgM ≥1:160 (345/485, 90.3%) IgG ≥1:160 (437/484, 71.1%)
Present	Israel (2005-2014)	128	<19	33 (25.8)	23 (17.9)	13 (10.2)	14 (10.9)	3 (2.3)	128 (100.0)	None	<1:160 (13, 13.7%) >1:1280 (14, 14.7%)

***** % of all patients with hematologic abnormalities

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