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Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Medicine

journal homepage: http://ees.elsevier.com/apjtm

Original research http://dx.doi.org/10.1016/j.apjtm.2015.11.009

Childhood brucellosis: Review of 317 cases

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ARTICLE INFO

Article history:
Received 15 Sep 2015
Received in revised form 20 Oct 2015
Accepted 3 Nov 2015
Available online 14 Nov 2015

Keywords:
Brucellosis
Children
Clinical manifestation
Treatment
Outcome

ABSTRACT

Objective: To describe the main epidemiological, clinical, and laboratory features, treatment options and outcome in children with brucellosis.

Methods: Retrospectively evaluated data were obtained from 317 pediatric patients with brucellosis that were treated at the University Clinic for Infectious Diseases and Febrile Conditions in Skopje, during the period from 1989 to 2011. The medical records and follow-up protocols were used for evaluation.

Results: Childhood brucellosis composed 317 (18.7%) of 1 691 patients with brucellosis. The patients were median 9 years old, ranging from 7 months to 14 years, and 201 (63.4%) were males. Family history was present in 197 (62.1%), and direct contact with animals occurred in 140 (44.2%) of the children. The dominant manifestations were fever in 248 (78.2%), joint pain in 228 (71.9%) and hepatomegaly in 216 (68.1%). Organ affection was present in 206 (65.0%) of the patients. One hundred and six (33.4%) of the patients were treated with combination composed of two, and 211 (66.6%) with three antimicrobial agents. Relapses were registered in 21 (6.6%), and therapeutic failures in 3 (0.9%) of the children.

Conclusions: In endemic regions childhood brucellosis represents a significant part of human cases. Wide spectrum of clinical manifestations, frequent affection of various organ systems and possibility of relapses show that brucellosis could be a serious disease in this age group. The presence of fever, joint pain, sweating, and affection of various systems in children from endemic regions should alert pediatricians for the possibility of brucellosis.

1. Introduction

Human brucellosis is a worldwide distributed zoonosis that is characterized with protean clinical manifestations [1]. The disease is mainly acquired by contact with infected animals and their products, ingestion of thermally unprocessed food from animal origin, and aerosol inhalation [2]. The way brucellosis sustains among humans in endemic regions is mainly based on the food tradition and husbandry practices [3,4]. In developed countries, brucellosis is a sporadic illness, and illegally imported unpasteurized dairy products and international travel in endemic regions play a significant role in disease acquirement. Not to underestimate as a possible way for disease achievement in these regions is professional acquisition, either in microbiological laboratories, or during close professional activities with animals [4–6].

All age groups are susceptible to human brucellosis [7–9]. It has been estimated that in endemic regions, quarter of the patients are younger than 14 years [1,10–13]. Actually the rate of childhood brucellosis in endemic regions is reported to be from 11% [14] to 56% [15]. Also, the existing literature is plenty with discrepancies concerning epidemiological and clinical characteristics as well as the outcome rates in children with brucellosis. The purpose of this paper is to find out the main clinical, epidemiological characteristics and outcome of childhood brucellosis in Republic of Macedonia as an endemic

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Peer review under responsibility of Hainan Medical College.

region. To our knowledge this is one of the largest series in literature with children suffering from brucellosis.

2. Materials and methods

We performed a retrospective analysis of medical records and follow-up protocols of 317 patients with brucellosis younger than 15 years. All of the patients were diagnosed and treated at the University Clinic for Infectious Diseases and Febrile Conditions in Skopje from January 1989 to December 2011. The study was approved by the Medical Faculty Ethic Committee.

The diagnosis of brucellosis was made on the basis of compatible clinical signs and symptoms in the presence of positive serological tests, namely, standard tube agglutination, *Brucella* Coombs test or the Brucellacapt assay, according to the study period. The corresponding titers considered positive were $\geq$1/160, $\geq$1/320 and > 1/320, respectively [16–19]. During the study period, bacteriological isolation was not routinely performed in the country.

Osteoarticular involvement was considered in the presence of inflammatory signs in any peripheral osteoarticular location, and/or inflammatory pain in any deep osteoarticular location accompanied by evidence of abnormalities with adequate imaging techniques [20]. Respiratory system involvement was accepted as the occurrence of conjunctivitis, sore throat, hoarseness, cough, dyspnea, chest pain, chest auscultator findings or abnormal chest X-ray. Gastrointestinal damage was registered with vomiting, diarrhea, abdominal discomfort, and abdominal tenderness on palpation. Liver involvement was evident with jaundice and/or at least 2-fold rise of alanin aminotransferase above upper normal limit. Orchitis and epididymitis were diagnosed by the presence of swelling and tenderness of the testis and epididymis. Neurobrucellosis was defined as an existence of central nervous system disturbance in combination with pathologic laboratory findings in the cerebrospinal fluid or imaging techniques, or as clinically and by electromyography proven peripheral neurological dysfunction. Cardiac involvement was detected by the presence of a cardiac murmur, EKG changes, or echocardiographic abnormalities. All of the above mentioned manifestations were considered to be of brucellar origin if it could not be explained and related with other diseases, if there was some association between their appearance and brucellosis course and if there was a positive response on administered antibrucellar treatment. A therapeutic failure was defined as an absence or a weak tendency for improvement of symptoms and signs attributed to the disease after 45 d of antibiotic treatment, and a relapse as the reappearance of disease symptoms and signs after the antibrucellar treatment was completed.

The patients were treated with combinations composed of either two or three of the following antimicrobials: oral tetracycline, 1 000–2 000 mg/day; oral doxycycline 100–200 mg/day (both in patients older than 8 years); oral rifampin 15–20 mg/(kg·d); oral trimethoprim/sulfamethoxazole 10–12 mg/(kg·d)/50–60 mg/(kg·d); intramuscular streptomycin 20–25 mg/(kg·d) and intramuscular gentamicin 5 mg/(kg·d). When used, tetracycline, doxycycline, trimethoprim/sulfamethoxazole and rifampin were administered for at least 45 d. Streptomycin was used for the first 14–30 d, and gentamicin for the first 7–10 d. In patients that manifested neurobrucellosis, myocarditis, or therapeutic failure, treatment duration was 60–180 d.

Patients were treated as inpatients or outpatients, depending on their age, disease severity, complications, medical infrastructure in the place of residency, and consent for hospital treatment. All patients underwent standard diagnostic protocol, comprising of detailed anamnestic data, physical examination and laboratory analysis, namely, hemoglobin, white blood cells, lymphocytes, blood glucose level, blood urea level, liver function tests, and in some patients broader investigations like erythrocyte sedimentation rate, platelets and C-reactive protein. The first months after completing the treatment patients were followed up once monthly, and afterwards in 2–6 months intervals. During the control check-ups clinical evaluation, laboratory and serology were evaluated.

Patient's age, illness duration prior to diagnosis, defervescence, and follow-up period are presented using median and range values. All other parameters are presented as frequencies and percentages. The *Chi*-squared test was used for comparison of examined variables. $P < 0.05$ was considered significant.

3. Results

Out of 1 691 patients with documented brucellar infection that were managed at the University Clinic for Infectious Diseases in Skopje during the investigated period, 317 (18.7%) were children. Their annual distribution during the investigated period is shown in Figure 1. Nine of the children (2.8%) were previously hospitalized and investigated in different departments due to unrecognized diagnosis.

As presented in Figure 2, 201 (63.4%) children were male and 116 (36.6%) female, with a median age of 9 years, ranging from 7 months to 14 years. Younger than 7 years (preschool age) were 98 (30.9%) patients and the remaining 219 (69.1%) were 7 years or older (school age). Males were 150 (68.5%) of the school and 51 (52.0%) of the preschool children ($P = 0.005$). Family history of brucellosis was evident in 197 (62.1%) patients. In 167 (52.7%) children brucellosis was acquired alimentary, in 140 (44.2%) there was direct contact with infected animals, whereas in 10 (3.1%) patients the route of disease acquisition remained unknown. One hundred and twenty three (56.2%) of the school children had direct contact with infected animals, whereas in preschool children this way of disease acquisition was found in 17 (17.4%) ($P < 0.001$). In 162 (51.1%) of the children the onset of brucellosis was registered during the period December–May, and in the remaining 155 (48.9%) it was during June–November. Animal contact was proved in 81 (50.0%) children with illness beginning during the period December–May, and in 59 (38.1%) in whom the first manifestations were during the period June–November ($P = 0.032$). In 113 (56.2%) of the male and in 49 (42.2%) of

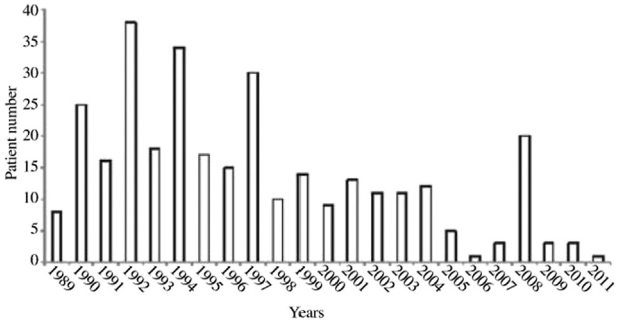

Figure 1. Annual distribution of childhood brucellosis from 1989 to 2011. Blank bars indicate pediatric cases with brucellosis.

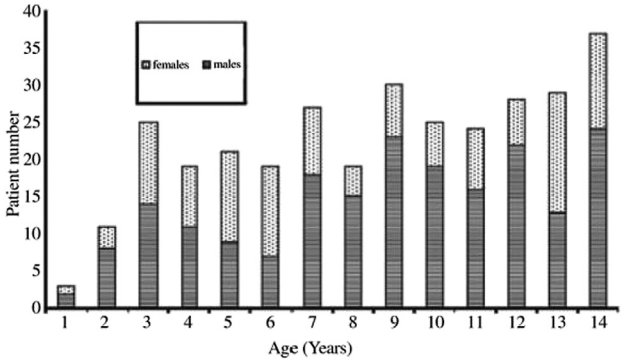

Figure 2. Sex and age distribution in 317 children with brucellosis. Dotted bars indicate females; Horizontal lines bars indicate males.

female patients, the beginning of the disease was during the period December–May ($P = 0.016$). Also, in 120 (54.8%) of the school age and in 42 (42.9%) of the preschool age group, brucellosis was manifested during the period December–May ($P = 0.049$).

The median illness duration prior to establishing the diagnosis was 21 d, ranging 3–360 d. In 244 (77.0%) patients the disease was recognized during the first month of the symptoms onset. Nine (2.8%) of the patients had co-infection at the time when diagnosis of brucellosis was confirmed, that is, three had helminthiasis, two rubella, two salmonellosis, and one of each tineacapitis and lambliasis. Co-morbidity was present in 8 (2.5%) children, that is, two with rachitis, and one of each with chronic otitis, chronic mastoiditis, sinusitis, bronchial asthma, celiac disease and epilepsy.

The dominant clinical manifestations in children with brucellosis were fever, joint pain, and hepatomegaly (Table 1) [9,14,21–30], and dominant laboratory parameters were elevated C-reactive protein and lymphocytosis (Table 2) [21,23–26,28,30–34]. Two hundred and four (64.4%) of the patients at admission showed the highest performed serological dilutions. Osteoarticular involvement was noted in 133 (42.0%) children, described separately [20], 34 (10.7%) had respiratory, 33 (10.4%) gastrointestinal manifestations, 8 (2.5%) had liver involvement and 12 (3.8%) manifested different forms of skin

Table 1
Clinical characteristics in children with brucellosis, in the present and other studies.

Reference number	Percent of patients reporting manifestation									
	Number of cases	Fever (symptom)	Malaise	Sweating	Arthralgia	Weight loss	Headache	Fever (sign)	Hepato-megaly	Spleno-megaly
[9]	53	90	98	72	83	NR	94	NR	42	55
[14]	48	87	77	79	67	56	47	NR	25	37
[21]	157	100	91	NR	25	NR	NR	NR	31	55
[22]	90	65	NR	19	86	16	NR	NR	23	18
[23]	147	39	17	19	61	NR	5	NR	5	5
[24]	200	70	67	22	74	67	NR	NR	28	25
[25]	102	91	60	19	73	48	11	NR	28	35
[26]	115	88	18	9	73	NR	7	91	13	12
[27]	32	94	28	NR	37	3	NR	NR	69	78
[28]	103	55	42	16	53	13	17	NR	43	38
[29]	52	81	19	15	14	8	2	NR	69	48
[30]	22	91	86	50	36	14	18	77	46	32
Present study [*n*(%)]	317	248(78)	191(60)	202(64)	228(72)	33(10)	105(33)	154(49)	216(68)	167(53)

NR: Not reported.

Table 2
Frequency of hematological and biochemical features in children with brucellosis, in the present and other studies.

Reference number	Percent of patients reporting results									
	Number of cases	ESR >20 mm/h	Hb ≤ 100 g/L	WBC $\geq 1 \times 10^{10}$/L	WBC $< 4 \times 10^{9}$/L	Ly > 40%	Platelets $< 1.5 \times 10^{11}$/L	PCP	ALT >40 U/L	CRP >5 mg/L
[21]	157	81	6	12	38	NR	28	NR	NR	NR
[23]	147	52	20	NR	14	NR	9	3	26	64
[24]	200	75	NR	14	30	92	2	NR	84	NR
[25]	102	68	33	0	30	NR	2	3	58	NR
[26]	115	74	25	23	9	NR	2	NR	NR	NR
[28]	103	62	17	14	8	NR	NR	NR	NR	NR
[30]	22	91	41	9	18	NR	14	NR	36	86
[31]	52	73	40	2	21	4	6	4	42	31
[32]	21	87	65	5	30	NR	NR	10	NR	NR
[33]	34	38	53	3	33	NR	12	NR	31	63
[34]	60	NR	43	20	38	83	NR	18	NR	NR
Present study [*n*(%)]	317	119(42)[a]	33(10)	19(6)	47(15)	201(63)	15(11)[b]	6(5)[b]	45(14)	114(79)[c]

NR: Not reported; ESR: Erythrocyte sedimentation rate; Hb: Hemoglobin; WBC: White blood cells; Ly: Lymphocytes; PCP: Pancytopenia; ALT: Alanine aminotransferase; CRP: C-reactive protein.
[a] Studied in 283 patients. [b] Studied in 132 patients. [c] Studied in 144 patients.

Table 3
Therapeutic options and relapses in 317 children with brucellosis.

Regimen	Number of treated patients	Relapses [*n*(%)]
R + D (T) + G (S)	18	2(11.1)
R + TMP-SMZ + G (S)	43	4(9.3)
D (T) + TMP-SMZ + G (S)	47	1(2.1)
R + D (T) + TMP-SMZ	103	8(7.8)
R + TMP-SMZ	74	4(5.4)
R + D (T)	19	2(10.5)
TMP-SMZ + G (S)	13	0(0)

R: rifampin; D: doxycycline; T: tetracycline; G: gentamicin; S: streptomycin; TMP-SMZ: trimethoprim/sulfamethoxazole.

eruption (macular, maculopapular, erythematous, papulovesicular, and petechial). Also, two patients were diagnosed with myocarditis, three manifested cutaneous vasculitis, two had testicular affection, whereas epistaxis, peripheral neuritis, central neuritis, meningitis, parotitis and mastitis were diagnosed in one of each patient.

As shown in Table 3, 106 (33.4%) of the patients were treated with two, and 211 (66.6%) with three antimicrobial agents. In 121 (38.2%) of children parenteral antimicrobial agents was used, whereas in 196 (61.8%) therapeutic combinations comprised entirely of per oral drugs. In 167 children (52.7%), most of them were with osteoarticular involvement and fever, and acetaminophen or ibuprofen was given for some time period. Depending on the clinical course and laboratory parameters, the treatment was sometimes supplemented with antimycotics, B group vitamin supplements, as well as parenteral rehydration. Corticosteroids were given in all patients with myocarditis, testicular affection, pancytopenia and neurobrucellosis and in two children with respiratory involvement until clinical and laboratory improvement was achieved.

The median defervescence was 3 d, ranging 1–20 d and the median follow-up period was 6 months, ranging 0–84 months. Relapses were seen in 21 (6.6%) children. Three patients with osteoarticular involvement experienced therapeutic failure, as described in other manuscript [20]. The rest of 293 (92.4%) were cured with only one therapeutic course. In seven children, at least 3 years post therapy and asymptomatic period with declining serology, emergence of clinical signs and symptoms with positive serological tests was seen, and this was considered to be a re-infection. We had no cases with fatal outcome.

4. Discussion

According to the incidence of brucellosis in the time period that has been evaluated in this manuscript, Republic of Macedonia was one of the leading states in the world [4]. The rate of pediatric patients with brucellosis we reported is comparable to the rate in certain regions of Turkey [9] and India [35], higher than in Greece [8], and lower than the incidence reported from certain Asian regions [27,36,37]. Concerning the male sex involvement and family history, our findings were within the previously reported ranges: 33%–79% [35,38] and 13.5%–73% [14,28] respectively. The disease acquisition according to the season is 54% during the period March–June in Greece [31], 71% during June–September in Israel [39], and predominately April–August in Iran [15,40] and Jordan [37]. The period December–May in Republic of Macedonia is generally considered to be the most intensive time with many different activities around animals (giving labor, milking, and slaughtering), whereas in the rest of the time the disease was mainly acquired through ingestion of young cheese prepared from unpasteurized milk. The predominant way of disease acquisition in school age male children through contact with animals in the period December–May, as well as high percentage of brucellosis family history which is evident in this study, resembles the children's living conditions and husbandry activities as a life style in shepherds' families in this endemic region.

The time we needed to ascertain the diagnosis of brucellosis is satisfactory and comparable with previously reported ones [29,41,42], suggestive that there is a good level of suspicion about brucellosis. Notably, early establishment of diagnosis is also due to the endemicity of the disease and its familiar distribution. Compared to others, one can find data about quicker [23,26,30,43,44] or longer [22,38] duration of the symptoms until the final diagnosis of brucellosis was done. As an entity, none of the children with brucellosis reviewed in our study fulfilled the criteria for fever of unknown origin [45,46], which is unlike to other studies from endemic regions [33,47].

The clinical and laboratory characteristic in childhood brucellosis in general are protean and non-specific, so they are not conclusive enough to guide the clinician, especially in the absence of epidemiological data [35,48]. It has been considered that childhood brucellosis produces mild to moderate disease, with exceptionally rare progress to chronicity [49] and mortality [26,40]. As presented, the reported frequencies of clinical and laboratory manifestations in children with brucellosis were within a wide range. We showed a lower percentage of patients with fever as a sign and also a lower percentage of patients with elevated erythrocyte sedimentation rate as the only declination from the already reported. Similar to other studies [23,42], this study shows that most of the patients at admission had maximal dilution of the titers of antibrucellar antibodies, which in the absence of microbiological methods significantly lessens the diagnosis.

Besides osteoarticular involvement, children with brucellosis quite often suffer from affection of the hematopoietic, respiratory (ranging 2%–75%) [9,14], gastrointestinal (ranging 2%–62%) [23,26], urogenital (ranging 2%–11%) [9,14,15], central nervous (ranging 2%–15%) system[14,22,31,32], skin (ranging 2%–26%) [9,26], and heart (ranging 2%–10%) [31,32,35]. In children with brucellosis many rare forms have been described, like endocarditis [14,24,35], myocarditis [24–26], pericarditis [32], nephritis [26,38], episcleritis, chorioretinitis [50], uveitis [32,38,50], cholecystitis, ataxia [42], peritonitis [42,51], central and peripheral neuritis [35,43], acute flaccid paralysis [40], cerebral pseudotumor [52], demyelination [53], depression [41], electrocardiographic changes, brain abscess, jaundice, leucemoid reaction, systolic murmur [31], epistaxis [33,48], and parotitis [42].

This study encircles the time period after 1986, the year in which WHO published the still currently used recommendations for the treatment of human brucellosis [54]. Nevertheless, as a result of some of our own insights, experience and tradition, most of our patients were treated with three antimicrobial agents. Even today, there are some contradictions about the treatment choice [30,49] and the treatment duration [13,24,29,31,49,55–57] in children.

Combined treatment with duration of at least 4 weeks in childhood brucellosis results with a wide range of relapses; from 0 to 32% [22,30,35,42,58,59]. The percentage of relapses we reported was alike in several other series with similar choice of therapeutic protocols [22,24,25,40,60]. It seems that relapses are not related to drug resistance [61,62] although one study mentioned higher frequency when drugs to which brucellae are resistant were used [44]. Nonetheless, comparing therapeutic outcome in different series is difficult, considering the differences in treatment duration, different drug regimens, the follow-up period, definitions of relapse, and maybe even the characteristics of the population and the infective agent. Maybe we should have in mind too the quality of the prescribed drugs used in the countries in transition. We accepted that patients who were lost of follow-up soon after treatment were cured, having in mind that for almost all of them our hospital was the only competent medical institution for this pathology. The small number of patients in some of the different therapeutic groups, as well as the retrospective character of this study, has incapacitated us to make more complex analysis of the therapeutic efficacy of the different drug combinations that were used in our patients.

In conclusion, in Republic of Macedonia, childhood brucellosis represents a significant part of human cases and is characterized with wide spectrum of clinical manifestations, high percentage of various organ involvements and appearance of relapses and therapeutical failures. As a result of children's life style and their engagement in everyday familiar activities, the children's sex and age is evidently associated with the season and the way in which brucellosis is acquired. Timely recognition as well as prompt and proper treatment of the disease gives hope to its favorable outcome.

Conflict of interest statement

We declare that we have no conflict of interest.

References

[1] Mousa ARM, Elhag KM, Khogali M, Marafie AA. The nature of human brucellosis in Kuwait: study of 379 cases. *Rev Infect Dis* 1988; **10**: 211-217.

[2] Bosilkovski M, Krteva L, Dimzova M, Kondova I. Brucellosis in 418 patients from the Balkan Peninsula: exposure-related differences in clinical manifestations, laboratory test results, and therapy outcome. *Int J Infect Dis* 2007; **11**: 342-347.

[3] Araj GF. Human brucellosis: a classical infectious disease with persistent diagnostic challenges. *Clin Lab Sci* 1999; **12**: 207-212.

[4] Pappas G, Papadimitriou P, Akritidis N, Christou L, Tsianos EV. The new global map of human brucellosis. *Lancet Infect Dis* 2006; **6**: 91-99.

[5] Young EJ. Brucellosis: current epidemiology, diagnosis, and management. *Curr Clin Top Infect Dis* 1995; **15**: 115-128.

[6] Pappas G, Panagopoulou P, Christou L, Akritidis N. Brucella as a biological weapon. *Cell Mol Life Sci* 2006; **63**: 2229-2236.

[7] Bosilkovski M, Krteva L, Dimzova M, Vidinic I, Sopova Z, Spasovska K. Human brucellosis in Macedonia–10 years of clinical experience in endemic region. *Croat Med J* 2010; **51**: 327-336.

[8] Andriopoulos P, Tsironi M, Deftereos S, Aessopos A, Assimakopoulos G. Acute brucellosis: presentation, diagnosis, and treatment of 144 cases. *Int J Infect Dis* 2007; **11**: 52-57.

[9] Gur A, Geyik MF, Dikici B, Nas K, Cevik R, Sarac J, et al. Complications of brucellosis in different age groups: a study of 283 cases in southeastern Anatolia of Turkey. *Yonsei Med J* 2003; **44**: 33-44.

[10] Shehabi A, Shakir K, el-Khateeb M, Qubain H, Fararjeh N, Shamat AR. Diagnosis and treatment of 106 cases of human brucellosis. *J Infect* 1990; **20**: 5-10.

[11] Ayatollahi J. Epidemiological, clinical, diagnostic and therapeutic survey of 686 cases of brucellosis. *Ann Saudi Med* 2004; **24**: 398-399.

[12] Akbayram S, Dogan M, Akgun C, Peker E, Parlak M, Caksen H, et al. An analysis of children with brucellosis associated with pancytopenia. *Pediatr Hematol Oncol* 2011; **28**: 203-208.

[13] Gotuzzo E, Carillo C. Brucella. In: Gorbach SL, Bartlett JG, Blacklow NR, editors. *Infectious diseases*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2004, p. 1837-1845.

[14] Madkour MM. Childhood brucellosis. In: Madkuor MM, editor. *Brucellosis*. Cambridge: Butterworths, University Press; 1989, p. 205-218.

[15] Feiz J, Sabbaghian H, Miralai M. Brucellosis due to *B. melitensis* in children. Clinical and epidemiologic observations on 95 patients studied in central Iran. *Clin Pediatr (Phila)* 1978; **17**: 904-907.

[16] Bosilkovski M, Katerina S, Zaklina S, Ivan V. The role of Brucellacapt test for follow-up patients with brucellosis. *Comp Immunol Microbiol Infect Dis* 2010; **33**: 435-442.

[17] Mile B, Valerija K, Krsto G, Ivan V, Ilir D, Nikola L. Doxycycline-rifampin versus doxycycline-rifampin-gentamicin in treatment of human brucellosis. *Trop Doct* 2012; **42**: 13-17.

[18] Bosilkovski M, Krteva L, Caparoska S, Dimzova M. Osteoarticular involvement in brucellosis: study of 196 cases in the Republic of Macedonia. *Croat Med J* 2004; **45**: 727-733.

[19] Bosilkovski M, Krteva L, Caparoska S, Dimzova M. Hip arthritis in brucellosis: a study of 33 cases in the Republic of Macedonia (FYROM). *Int J Clin Pract* 2004; **58**: 1023-1027.

[20] Bosilkovski M, Kirova-Urosevic V, Cekovska Z, Labacevski N, Cvetanovska M, Rangelov G, et al. Osteoarticular involvement in childhood brucellosis: experience with 133 cases in an endemic region. *Pediatr Infect Dis J* 2013; **32**: 815-819.

[21] Benjamin B, Annobil SH. Childhood brucellosis in southwestern Saudi Arabia: a 5-year experience. *J Trop Pediatr* 1992; **38**: 167-172.

[22] Tanir G, Tufekci SB, Tuygun N. Presentation, complications, and treatment outcome of brucellosis in Turkish children. *Pediatr Int* 2009; **51**: 114-119.

[23] Okur M, Erbey F, Bektas MS, Kaya A, Dogan M, Acar MN, et al. Retrospective clinical and laboratory evaluation of children with brucellosis. *Pediatr Int* 2012; **54**: 215-218.

[24] Sharda DC, Lubani M. A study of brucellosis in childhood. *Clin Pediatr (Phila)* 1986; **25**: 492-495.

[25] al-Eissa YA, Kambal AM, al-Nasser MN, al-Habib SA, al-Fawaz IM, al-Zamil FA. Childhood brucellosis: a study of 102 cases. *Pediatr Infect Dis J* 1990; **9**: 74-79.

[26] Shaalan MA, Memish ZA, Mahmoud SA, Alomari A, Khan MY, Almuneef M, et al. Brucellosis in children: clinical observations in 115 cases. *Int J Infect Dis* 2002; **6**: 182-186.

[27] Yinnon AM, Morali GA, Goren A, Rudensky B, Isacsohn M, Michel J, et al. Effect of age and duration of disease on the clinical manifestations of brucellosis. A study of 73 consecutive patients in Israel. *Isr J Med Sci* 1993; **29**: 11-16.

[28] Caksen H, Arslan S, Oner AF, Cesur Y, Ceylan A, Atas B, et al. Childhood brucellosis is still a severe problem in the eastern region of Turkey. *Trop Doct* 2002; **32**: 91-92.

[29] Giannakopoulos I, Nikolakopoulou NM, Eliopoulou M, Ellina A, Kolonitsiou F, Papanastasiou DA. Presentation of childhood brucellosis in Western Greece. *Jpn J Infect Dis* 2006; **59**: 160-163.

[30] Ulug M, Yaman Y, Yapici F, Can-Ulug N. Clinical and laboratory features complications and treatment outcome of brucellosis in childhood and review of the literature. *Turk J Pediatr* 2011; **53**: 413-424.

[31] Galanakis E, Bourantas KL, Leveidiotou S, Lapatsanis PD. Childhood brucellosis in north-western Greece: a retrospective analysis. *Eur J Pediatr* 1996; **155**: 1-6.

[32] Logan LK, Jacobs NM, McAuley JB, Weinstein RA, Anderson EJ. A multicenter retrospective study of childhood brucellosis in Chicago, Illinois from 1986 to 2008. *Int J Infect Dis* 2011; **15**: e812-817.

[33] Fanni F, Shahbaznejad L, Pourakbari B, Mahmoudi S, Mamishi S. Clinical manifestations, laboratory findings, and therapeutic regimen in hospitalized children with brucellosis in an Iranian Referral Children Medical Centre. *J Health Popul Nutr* 2013; **31**: 218-222.
[34] El-Koumi MA, Afify M, Al-Zahrani SH. A prospective study of brucellosis in children: relative frequency of pancytopenia. *Mediterr J Hematol Infect Dis* 2013; **5**: e2013011.
[35] Mantur BG, Akki AS, Mangalgi SS, Patil SV, Gobbur RH, Peerapur BV. Childhood brucellosis–a microbiological, epidemiological and clinical study. *J Trop Pediatr* 2004; **50**: 153-157.
[36] Sabbaghian H, Nadim A. Epidemiology of human brucellosis in Isfahan. *Iran J Hyg (Lond)* 1974; **73**: 221-228.
[37] Khuri-Bulos NA, Daoud AH, Azab SM. Treatment of childhood brucellosis: results of a prospective trial on 113 children. *Pediatr Infect Dis J* 1993; **12**: 377-381.
[38] Gedalia A, Watemberg N, Rothschild M. Childhood brucellosis in the Negev. *Harefuah* 1990; **119**: 313-315.
[39] Gottesman G, Vanunu D, Maayan MC, Lang R, Uziel Y, Sagi H, et al. Childhood brucellosis in Israel. *Pediatr Infect Dis J* 1996; **15**: 610-615.
[40] Sasan MS, Nateghi M, Bonyadi B, Aelami MH. Clinical features and long term prognosis of childhood brucellosis in northeast Iran. *Iran J Pediatr* 2012; **22**: 319-325.
[41] Shen MW. Diagnostic and therapeutic challenges of childhood brucellosis in a nonendemic country. *Pediatrics* 2008; **121**: e1178-1183.
[42] El-Amin EO, George L, Kutty NK, Sharma PP, Choithramani RS, Jhaveri VP, et al. Brucellosis in children of Dhofar Region. *Oman Saudi Med J* 2001; **22**: 610-615.
[43] Tsolia M, Drakonaki S, Messaritaki A, Farmakakis T, Kostaki M, Tsapra H, et al. Clinical features, complications and treatment outcome of childhood brucellosis in central Greece. *J Infect* 2002; **44**: 257-262.
[44] Almuneef M, Memish ZA, Al Shaalan M, Al Banyan E, Al-Alola S, Balkhy HH. Brucella melitensis bacteremia in children: review of 62 cases. *J Chemother* 2003; **15**: 76-80.
[45] Leung AK, Robson WL. Fever in childhood: part 2: fever of unknown origin. *Can Fam Physician* 1992; **38**: 1841-1845.
[46] Akpede GO, Akenzua GI. Management of children with prolonged fever of unknown origin and difficulties in the management of fever of unknown origin in children in developing countries. *Paediatr Drugs* 2001; **3**: 247-262.
[47] Ciftdogan DY, Bayram N, Vardar F. Brucellosis as a cause of fever of unknown origin in children admitted to a tertiary hospital in the Aegean region of Turkey. *Vector Borne Zoonotic Dis* 2011; **1**: 1037-1040.
[48] Street L Jr, Grant WW, Alva JD. Brucellosis in childhood. *Pediatrics* 1975; **55**: 416-421.
[49] Gotuzzo E. Brucellosis. In: Guerrant RL, Walker DH, Weller PF, editors. *Tropical infectious diseases. Principles, pathogens, and practice*. Philadelphia: Churchill Livingstone; 1999, p. 498-505.
[50] Mohammadi Z, Dehghani A, Ghanbari HO, Akhlaghi MR, Nasrollahi K, Salam H. Ocular manifestations in a child with systemic brucellosis. *J Res Med Sci* 2014; **19**: 677-679.
[51] Lapphral K, Leelaporn A, Vanprapar N, Chearskul P, Sawawiboon N, Wittawatmongkol O, et al. First case report of brucellosis in a child in Thailand. *Southeast Asian J Trop Med Public Health* 2014; **45**: 890-896.
[52] Unknown. A rare presentation of neurobrucellosis in a child with recurrent transient ischemic attacks and pseudotumorcerebri (A case report and review of literature). *Iran J Child Neurol* 2014; **8**: 65-69.
[53] Bektas O, Ozdemir H, Yılmaz A, Fitoz S, Ciftci E, Ince E, et al. An unusual case of neurobrucellosis presenting as demyelination disorder. *Turk J Pediatr* 2013; **55**: 210-213.
[54] Joint Food and Agriculture Organization (FAO), World Health Organization (WHO). *FAO-WHO expert committee on brucellosis (sixth report)*. WHO technical report series, no 740. Geneva: World Health Organization; 1986.
[55] Llorens-Terol J, Busquets RM. Brucellosis treated with rifampicin. *Arch Dis Child* 1980; **55**: 486-488.
[56] Nabi G, Mir NA. Brucellosis in pediatric patients: a review of 114 cases from Asir region. *Ann Saudi Med* 1992; **12**: 286-288.
[57] Lubani MM, Dudin KI, Sharda DC, Ndhar DS, Araj GF, Hafez HA, et al. A multicenter therapeutic study of 1100 children with brucellosis. *Pediatr Infect Dis J* 1989; **8**: 75-78.
[58] Issa H, Jamal M. A study of brucellosis in childhood. Brucellosis in children in south Jordan. *East Mediterr Health J* 1999; **5**: 895-902.
[59] Khalili M, Sharifi-Mood B, Metanat M, Salehi M. Epidemiology, clinical presentation, and treatment outcome of brucellosis among children. *Int J Infect* 2014; **1**: e21570.
[60] Roushan MR, Mohraz M, Janmohammadi N, Hajiahmadi M. Efficacy of cotrimoxazole and rifampin for 6 or 8 weeks of therapy in childhood brucellosis. *Pediatr Infect Dis J* 2006; **25**: 544-545.
[61] Maves RC, Castillo R, Guillen A, Espinosa B, Meza R, Espinoza N, et al. Antimicrobial susceptibility of *Brucella melitensis* isolates in Peru. *Antimicrob Agents Chemother* 2011; **55**: 1279-1281.
[62] Ariza J, Corredoira J, Pallares R, Viladrich PF, Rufi G, Pujol M, et al. Characteristics of and risk factors for relapse of brucellosis in humans. *Clin Infect Dis* 1995; **20**: 1241-1249.