Original Article

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Clinical Features and Long Term Prognosis of Childhood Brucellosis in Northeast Iran

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Abstract

Objective: Brucellosis is a prevalent disorder in children of developing countries. The aim of this study is to describe the epidemiology and long term prognosis of Brucellosis in Khorasan, Iran.

Methods: This is a descriptive cross sectional study (from November 2003 up to February 2006), the subjects of which are composed of 82 patients (from Imam Reza hospital, Mashhad, and Health Center of Kashmar). In this study the diagnosis of Brucellosis is based on serology accompanied with clinical signs and symptoms. Our strategy for duration of treatment was to treat all patients for at least 6 weeks. We followed the patients by phone and if necessary by visiting.

Findings: During 38 months we had 82 children with Brucellosis. The mean age was 8.02 y, and 40% of them were girls (M/F=1.21). Summer with 45.9% of the cases was the peak season. History of consuming raw dairy products, close contact with farm animals, living in village and Brucellosis in family was found in 91.6%, 76%, 70.24% and 41.1% of the cases respectively. The presenting symptom in 79.7% of the cases was joint pain, 72.9% had history of fever during the course of the disease. Arthritis, splenomegaly and lymphadenopathy were found in 60.97%, 16.9%, 7.5%, of patients respectively. The therapeutic regimen of 48.7% of our patients was Co-trimoxazole and rifampin. We followed 74% of the patients for at least 3 years which showed the relapse rate of 6.5 %. There was a case of reinfection, a patient with residual sequel and one death related to Brucellosis in our case series.

Conclusion: Brucellosis is still a common disease in our children and at least a risk factor for it can be found in the history of almost all cases of pediatric Brucellosis. With at least six weeks treatment with two antibiotics and with close follow up, we can decrease the relapse rate in pediatric Brucellosis to zero, even without repeating the serology during or after treatment.

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Key Words: Brucellosis; Children; Prognosis; Epidemiology

Introduction

Iran has been the second country in the world for the prevalence of brucellosis [1]. In our country *Brucella melitensis* is the main cause of human brucellosis. In endemic regions specialty when *B. melitensis* is prevalent, children account for up to 25% of cases of human brucellosis [2]. According to

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CDC case definition, in clinically and epidemiologically compatible cases, brucellosis can be confirmed by serology only when there is a fourfold rise in Brucella agglutination titer between acute- and convalescent-phase (at least 2 weeks apart), otherwise in a symptomatic person a single titer of ≥160 is considered as a probable case [2], but according to the Iranian national guideline for diagnosis of brucellosis (our cases are defined according to it), in symptomatic persons without previous history of brucellosis, Standard Tube Agglutination titer(STA) ≥1/80 is diagnostic for brucellosis. This is because antigens which are used in Wright STA test are *Brucella abortous* (BA) antigens but brucellosis in Iran (like in other endemic countries in the Middle East) is almost always caused by *Brucella melitensis* (BM). The agglutination of anti BM antibodies with BA antigens is weaker than BA antigens and BA antibodies agglutination, therefore many authors suggest that in endemic regions (in symptomatic persons without previous history of brucellosis), STA titer ≥1/80 is diagnostic for brucellosis [3-9]. The other reason for decreasing the cut off for Wright test in endemic areas is the statics rule that says the Positive Predictive Value (PPV) of a test has direct relation with the prevalence of the disease in the population.

This article is a report of clinical features of children with brucellosis in Khorasan (Northeast Iran). The province Khorasane Razavi has 4,700,000 inhabitants, Mashhad (the capital of it) is the second city of Iran with a population of 1,850,000. Kashmar is a city 250 km in south west of Mashhad with 121000 inhabitants. In Khorasan 38.8% of the population live in rural areas. According to the report of the health center of the Great Khorasan (2005) the incidence of human brucellosis in the province was 3000-5000 cases per year.

Subjects and Methods

This is a descriptive cross sectional study, the subjects of which are composed of 2 groups of patients, the first group consist of 59 children (0-15 y) with brucellosis who were visited by the author (from January 2003 up to February 2006) in the Pediatric Infectious Diseases clinic or ward of Imam Reza hospital (Mashhad), and the second group is composed of 25 children from Kashmar who were reported to the health center of the city by different doctors from January 2004 up to December 2005. Cases with simultaneous positive cultures with other organisms and cases with incomplete data were excluded.

In this study the diagnosis of brucellosis is based on serology (Wright ≥1/80, Coombs Wright ≥1/80, 2ME≥1/40 and rose Bengal) accompanied with suggestive clinical signs and symptoms.

Our strategy for duration of treatment (in Mashhad) was to treat all patients for at least 6 weeks and/or 4 weeks after resolution of all signs and symptoms, without asking 2-Mercapto Ethanol (2ME) test before or after stopping antibiotics. The Kashmar group was treated according to national protocol for 8 weeks but we are not sure about the compliance of their patients. We followed the patients by phone and if necessary by visiting in clinic in November 2008.

Findings

During 38 months (November 2003 up to December 2006) we had 82 children with brucellosis. The mean age was 8.02 y (10 m to 16 y), the mean age of Kashmar and Mashhad group was 9.7 y and 7.19 y respectively. Forty percent of the children were girls (M/F=1.21). Summer with 45.9% of the cases was the peak season and winter with only 6.8% was the nadir. History of drinking raw milk or having unpasteurized dairy products, direct contact with farm animals and brucellosis in family was found in 91.6% (55 of 60), 76% (19 of 25) and 41.1% (28 of 68) of the cases respectively, 70.2% of the cases were rural. We had three shepherds (7 to 16 years old) in our group. At least one of the above risk factors was found in 98.73% (78 of 79) of the cases (Table 1).

The chief complaint of 79.7 % (67 of 84) of the cases was joint pain and/or limping. Fever

Table 1: Risk factors for brucellosis in our children

Risk Factor	Frequency
Consumption of unpasteurized dairy products (n=60)	55 (91.6%)
Direct contact with farm animals (n=25)	19 (76%)
Brucellosis in family members (n=68)	28 (41.1%)
Villager (n=74)	52(70.24%)
Any of the above risk factors (n=79)	78 (98.73%)

accompanied with joint pain and/or limping was the main presentation in 28 (32.9%) cases. Most (72.9%) of our patients had history of fever during the course of their brucellosis, but only in 5% (4 of 84) fever was the chief complain and the dominant picture of the disease (the typhoidal type of brucellosis). Generalized lymphadenopathy, acute flaccid paralysis and abdominal pain each occurred in one patient as the chief complaint.

In physical examination arthritis, splenomegaly, lymphadenopathy and vertebral osteomyeltis were seen in 60.97% (50 of 82), 16.9% (9 of 53), 7.5% (3 of 40) and 2.3% (2 of 82) of patients respectively. Of 50 children who presented with arthritis 36 (72%) had mono arthritis; knee (24 patients) and hip (23 cases) were the most common involved joints (Table 2).

Blood, Urine and joint fluid culture was done for 12, 13 and 5 cases respectively and all of them were negative, other laboratory findings of the patients are shown in Table 3.

The therapeutic regimen of 48.7% (40 of 82) of our patients was Co-trimoxazole and rifampin, seven (8.5%) cases received Doxycycline-Aminoglycoside for the first 2-3 weeks and then Doxy–rifampin, four cases got Co-trimoxazole, rifampin plus gentamicin for the first 2 weeks and 2 cases were treated by Doxy plus rifampin. We treated all patients for at least 6 weeks.

Surgical intervention was done in 2 (2.3%) patients (arthrotomy and hemicollectomy each in one patient). The later was a 10 years old rural boy who was admitted in a local hospital with fever, bloody diarrhea and abdominal pain. He underwent laparotomy with diagnosis of appendicitis but the surgeon found patchy gangrenous lesions of right colon and right hemicollectomy was done (which showed nonspecific colitis in pathology), after surgery it was found that the serologic test for brucellosis is positive (Wright 1/640, 2ME 1/640) and he was treated for brucellosis. We followed the boy for 3 years, he didn't have any relapse of colitis (which rules out inflammatory bowel diseases).

Table 2: Clinical findings of brucellosis in our children

Variable		Total number= 84
Mean Age		8.02 y (10m-16y)
Season	Summer	45.9%
	Winter	6.8%
Male/Female ratio		1.21
Chief Complaint	Joint pain (± Limping)	79.7%
	Fever + Joint pain (± Limping)	(32.9%)
	Fever	5% (4 of 84)
	Generalized Lymphadenopathy	1 case
	Flaccid Paralysis	1 case
	Abdominal Pain	1case
Fever during the disorder		72.9%
Surgical Treatment		2 (2.3%)
Relapse		4 (6.5%)
Reinfection (Recurrence)		1 (1.6%)
Persistent Sequels		1 (1.6%)
Death		1 case (1.6%)

Table 3: Laboratory findings of children with brucellosis in Khorasan

Test	Result
Platelet (mean)	291600/mm³ (13700-778000)
Thrombocytopenia (PLT<150000)	8.1% (3 of 37)
Hemoglobulin (mean)	11.4gr/100 (9-14.7)
WBC (mean)	8671/mm³ (3900-15700)
Leukocytosis (WBC>15000)	2.3%
PMN>75%	2.3%
ESR (mean)	36mm/h (3-97mm/h)
ESR ≥50 mm/h	17.1% (6 of 35)
CRP	Negative in 46.1%
Normal inflammation markers (ESR and CRP and WBC)	29.16%

WBC: White Blood Cell; PMN: Polymorphonuclear; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein

There was one death related to brucellosis in our cases. This was an 8 year old girl with sacroileitis who developed Drug-induced Hypersensitivity Syndrome (DIHS). She presented with fever, erythroderma, generalized lymph-adenopathy and hepatosplenomegaly at the third week of treatment for brucellosis (with Co-trimoxasole and rifampicin). She was admitted for DIHS, all the antibiotics were stopped and she was doing well but at the 9th day of admission she suddenly expired with clinical diagnosis of nosocomial septic shock.

We followed 74.39% (61 of 82) of the patients for at least 3 years (and up to 6 years) after the treatment, four (6.5%) of them experienced relapse within 3 moths after the first treatment. All of the relapses were in Kashmar group. Thus the relapse rate in Kashmar group was 16% and in Mashhad 0%. One of the relapse cases was a 15 year old boy in whom relapse was in the form of orchioepididymitis. Of 61 cases with long term follow up only one (1.6%) case had residual sequelae due to brucellosis. She is a 13 year old girl who presented with acute flaccid paralysis in 2002 (at age of 7 years) and was discharged with the final diagnosis of brucellosis complicated with Guillain-Barre disease. After 6 years of follow up at October 2008 she walks to school independently but she has some degree of residual weakness. There was one case of recurrence or reinfection (brucellosis after more than 3 months of the first treatment) in our group which happened four years after the first episode of brucellosis.

Discussion

In Khorasan 38.8% of population live in rural areas but our study shows that 70.2% of children with brucellosis are village residents, in Greece and Turkey too, most cases of pediatric brucellosis are from rural areas [10,11]. This is a sign of partial control of brucellosis in our country which is mostly due to industrialization of dairies production in the last decade. Now the great majority of dairy products in the cities are from modern automatic dairy factories which are under strict control by health system. In rural areas of Khorasan people usually boil the milk before use but drinking fresh milk is not rare and especially cheese is made from raw milk. In highly endemic situations where non pasteurized dairy products are prevalent in cities, there is not a predominance of rural people among brucellosis cases and even the majority of cases are city residents [12].

Pediatric brucellosis is a perennial disorder, and seasonal prevalence of brucellosis has not been noticed by many authors [1,13-15] but some authors (similar to us) have shown that the disorder is more common in spring and summer [16,17,18,19,20,21]. In these seasons un-pasteurized dairy products from sheep and goats can be found in local bazaars. The seasonal prevalence is more obvious for brucellosis from sheep and goat than from cows, possibly because of the longer lactation period in cattle.

Unlike adult brucellosis which is more like an occupational disorder and has a strong male

predominance, pediatric brucellosis is mostly a food borne disease with no significant sex dominance [16,17,22-24]. The case series of pediatric brucellosis which have reported a strong male predominance (m/f=3) have a high proportion (>40%) of young shepherds in them and hence their m/f ratio is like an occupational disorder [26]. There is only one case series of pediatric brucellosis which has shown female predominance [25].

The classic risk factors for pediatric brucellosis are consumption of unpasteurized dairy products and direct contact with farm animals. Sofian in a report from Iran has shown that positive family history for brucellosis is the most important and specific predictor for pediatric brucellosis and they have recommended to screen family members of every patient with brucellosis [27]. History of brucellosis in first degree families has been reported in 15.6% to 47% of pediatric brucellosis case series [11,12]. Absence of any risk factor for brucellosis has been reported in 1.3% to 9.6% of pediatric brucellosis cases. This rate is 1.2% in our study, therefore the Negative Predictive Value(NPV) of absence of any risk factor, for diagnosis of pediatric brucellosis is high [10,25,26].

Although in developed countries brucellosis is mainly a disorder of immigrated minorities [1,16,22], in our case series we had only one (1.5%) Afghan refugee which shows that the disease is still endemic in Iranian population.

The typical clinical presentation of pediatric brucellosis is joint complaint (limping, arthralgia, arthritis) accompanied with fever, the prevalence of these has been reported 41%-85% and 73%-91% respectively in different reports [22-26].

Screening tests for inflammation (CRP, CBC, ESR) are not very helpful in the diagnosis of pediatric brucellosis, sever leukocytosis (WBC >20500) and very high ESR (>100) almost never occur in brucellosis [10,17,22]. Normal CRP is very common, WBC is normal or almost normal in most patients and ESR is normal or moderately increased [13,22]. In endemic regions when a child with a systemic illness has no abnormal screening test of inflammation, brucellosis is a good differential diagnosis (as it was seen in 29% of the cases in our study).

The relapse rate in pediatric brucellosis is between zero to 85% depending on antibiotic regimen (type of antibiotics and duration of therapy) [17,22,25,26]. No relapse has been reported with TMP-SMX and rifampicin (8-12 weeks) plus streptomycin (3 weeks) and with Doxycycline +rifampicin for six weeks+gentamicin for 5-7 days. Relapse rate of 85% has occurred with two antibiotics for less than 3 weeks [12,26]. With treatment regimens of 6 weeks and in patients with mean age of seven years (1-9 y), like ours, the relapse rate is 7.4%-8.1% [11,12,25]. The main cause of relapse is premature stopping of medicines due to inappropriate regimens or patient incompliance and almost always the relapse can be treated successfully with the same regimen but longer duration [1,17,25] We couldn't find any connection between age, clinical presentation and the Wright titer with relapse rate in our case group. The great disparity of relapse rate between Mashhad and Kashmar group in our study may be referred to more frequent re exposure to contaminated dairy product (and hence reinfection) and also less compliance with the medicines in rural communities in comparison to the city.

Most authors do not recommend serologic test before stopping medicines (as a guide for termination of the therapy) or after it (for early detection of relapse) [1,13-15,18], but the opinion of a few authors is that serologic follow up can be used to show the patient response to therapy and after ending of therapy for early detection of relapse [28]. In our country some of the experts do not stop the medicines until they have a negative or low (<1/40) 2ME test and some of them (like us) prefer to treat all patients for at least 6 weeks and after at least one month of being asymptomatic, discontinue it without any serologic follow up. Absence of any relapse in the Mashhad group of our study which were treated according to the latter strategy makes it more acceptable. Navarro and colleagues followed brucellosis patients after treatment completion with quantitative PCR (Q-PCR) and found that many asymptomatic patients had positive Q-PCR at the cessation of therapy and during follow-up without experiencing relapse. They concluded that a positive Q-PCR from an asymptomatic patient, recently treated with appropriate antibiotic does not necessarily

warrant further treatment [28].

Brucellosis is rarely a killing disorder in children. In adults although the mortality is low, endocarditis remains the main cause of death in brucellosis [29], but in children endocarditis of any cause is rare and the few reported cases of endocarditis in pediatric brucellosis have not shown any mortality [30]. Encephalitis, encephalopathy, and CNS hemorrhage due to ITP are the only 3 cases of death in pediatric brucellosis that we could find in Pubmed search and our case (death due to adverse drug reaction) will probably be the 4th reported death in children due to brucellosis [3,28].

The main limitation of this study is that all of the diagnoses are based on serology and there is no culture confirmed case. Although culture is the most definitive diagnostic test for brucellosis, in daily practice in endemic areas serology is the main diagnostic lab test, because bacteremia in brucellosis is low grade, the organism grows slowly and working with it has a significant contamination risk for the laboratory staff [2,9].

Conclusion

We conclude that brucellosis is still a common problem in our rural children and at least an epidemiologic risk factor for brucellosis can be found in the history of almost all cases of pediatric brucellosis. The problem of relapse which is a common event in brucellosis can be decreased to zero if we treat the children for at least six weeks with two antibiotics and with close follow up, even without repeating the serology during or after treatment.

Conflict of Interest: None

References

1. Pappas G, Akritidis N, Bosilkovski M, Tsianos E. Brucellosis. *N Engl J Med* 2005;352(22):2325-36.
2. Case definitions for infectious conditions under public health surveillance. Centers for Disease Control and Prevention. MMWR Recomm Rep. 1997;46(RR-10):1-55.
3. Caksen H, Odabaş D, Köse D, Anlar O. A fatal case of Brucellosis displaying an atypical clinical course. *J Emerg Med* 2003;25(4):472-4.
4. Zamani A, Daneshjoo Kh. Brucella antibody titer (Wright's test) in healthy primary school children in Tehran. *Iran J Pediatr* 2005;15(3):249-54.
5. Hosseini SMJ, Hosseini Shokouh SJ, Alishirei GH, et al. Epidemiology of human brucellosis in Ferdows, Sarayan and Boshrooyeh counties of southern Khorasan province in 2004-2005. *J Army Uni Med Sci IR Iran* 2009;7(2):117-22. (In Persian)
6. Mantecón L, Gutiérrez MP, Zarzosa P, et al. Influence of brucellosis history on serological diagnosis and evolution of patients with acute brucellosis. *J Infect* 2008; 57(5):397-403.
7. Gotuzzo E. Brucellosis. In: Guerrant R, Walker D, Waller P (eds). Tropical Infectious Diseases, Principles, Pathogens and Practice. 1st ed. Philadelphia: Chirchill Livingstone. 1999; Pp: 498-505.
8. Ajami A, Nasrolahi M, Sharif M. Comparison of serological methods for diagnosis of Brucellosis. *J Med Faculty Guilan Uni Med Sci* 2006;14(56):74-79. (In Persian)
9. Wallach J. Interpretation of diagnostic test. 5th ed. Boston: Little, brown; 1993; P: 23.
10. Giannakopoulos I, Nikolakopoulou NM, Eliopoulou M, et al. Presentation of childhood Brucellosis in Western Greece. *Jpn J Infect Dis* 2006;59(3):160-3.
11. Tanir G, Tufekci SB, Tuygun N. Presentation, complications, and treatment outcome of Brucellosis in Turkish children. *Pediatr Int* 2009; 51(1):114-9.
12. Al-Eissa YA, Kambal AM, al-Nasser MN, et al. Childhood brucellosis: a study of 102 cases. *Pediatr Infect Dis J* 1990;9(2):74-9.
13. Young EJ. Brucella species. In: Mandell, Douglas, and Bennett (eds). Principles and Practice of Infectious Diseases. 7th ed. Philadelphia: Chirchill Livingstone. 2009. Pp:2921-25
14. Young EJ. Brucellosis. In: Feigin,Cherry, Demmler, Kaplan (eds). Textbook of Pediatric Infectious Diseases. 6th ed. Philadelphia: Saunders. 2009, Pp:1678-83
15. Schutze GE, Jacobs RE. Brucella. In: Kliegman RM, Behrman RE, Jenson HB, et al. Nelson Textbook of Pediatrics. 18th ed. Philadelphia: Saunders 2007; Pp: 1214-6.
16. Dahouk SA, Neubauer H, Hensel A, et al. Changing epidemiology of human Brucellosis, Germany,

1962-2005. *Emerg Infect Dis* 2007;13(12):1895-900.

17. Gottesman G, Vanunu D, Maayan MC, et al. Childhood brucellosis in Israel. *Pediatr Infect Dis J* 1996;15(7):610-5.
18. Corbel MJ. Brucellosis in humans and animals. World Health Organization 2006. Available at: http://www.who.int/csr/resources/publications /Brucellosis. Access date: Aug 2010.
19. Sofizade A, Gorbani M, Salahi R, et al. Epidemiological characteristics of brucellosis in Kalale, Golestan Province of Iran (2003-2007). *J Gorgan Bouyeh Faculty Nurs & Midwifery 2*008; 14(5):8-15. (In Persian)
20. Kozukeev TB, Ajeilat S, Maes E, et al. Centers for Disease Control and Prevention (CDC). Risk factors for brucellosis--Leylek and Kadamjay districts, Batken Oblast, Kyrgyzstan, January-November, 2003. *MMWR Morb Mortal Wkly Rep* 2006;28:55(Suppl 1):31-4.
21. Buzgan T, Karahocagil MK, Irmak H, et al. Clinical manifestations and complications in 1028 cases of brucellosis: a retrospective evaluation and review of the literature. *Int J Infect Dis* 2010; 14(6):e469-78.
22. Shen MW. Diagnostic and therapeutic challenges of childhood brucellosis in a nonendemic country. *Pediatrics* 2008;121(5):e1178-83.
23. 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* 1978;17(12): 904-7
24. Hassanjani-Roshan MR, Zahed-Pasha Y. Efficacy of Co-trimoxazole and Rifampine in treatment of childhood Brucellosis. J Babol Uni Med Scis 2000; 8(2):17-20. (In Persian)
25. Al-Eissa YA, Kambal AM, Alrabeeah AA, et al. Osteoarticular brucellosis in children. *Ann Rheum Dis* 1990; 49(11):896-900.
26. Mantur BG, Akki AS, Mangalgi SS, et al. Childhood Brucellosis a microbiological, epidemiological and clinical study. *J Trop Pediatr* 2004;50(3): 153-7.
27. Sofian M, Aghakhani A, Velayati AA, et al. Risk factors for human brucellosis in Iran: a case-control study. *Int J Infect Dis* 2008;12(2):157-61.
28. Navarro E, Segura JC, Castaño MJ, Solera J. Use of real-time quantitative polymerase chain reaction to monitor the evolution of Brucella melitensis DNA load during therapy and post-therapy follow-up in patients with brucellosis. *Clin Infect Dis* 2006 1;42(9):1266-73.
29. Al-Nassir W. Brucellosis. E Medicine 2011 Available at: http://emedicine.medscape.com/ article/213430-overview. Access date: May 2011.
30. Lubani M, Sharda D, Helin I. Cardiac manifestations in Brucellosis. *Arch Dis Child* 1986; 61(6):569-72.