BRUCELLOSIS: REVIEW OF CLINICAL AND LABORATORY FEATURES AND THERAPEUTIC REGIMENS IN 44 CHILDREN

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Abstract- Brucellosis is not uncommon in children in endemic areas. We described clinical and laboratory features and therapeutic regimens for brucellosis in children under 14 who admitted in the Pediatric Medical Center Hospital, Tehran, Iran from March 1988 until February 2001. The male: female ratio was 2:1. Family history of brucellosis and consumption of un-pasteurized milk and dairy products was positive in 20.4% and 65.9%, respectively. The common clinical findings were arthritis (79.5%), fever (77.4%), anorexia (61.4%), sweating (52.3%), splenomegaly (43.2%), hepatomegaly (34.1%) and lymphadenopathy (13.65). Anemia, leukopenia and thrombocytopenia were recorded in 56.8%, 31.8% and 9.1%, respectively. Out of all patients, seropositivity rate for brucellosis was found in 97.7% using serum agglutination test. Culture of blood and bone marrow specimen were positive in 30% and 50% of samples obtained, respectively. Rifampin and co-trimoxazole were the most commonly used combination in 68.1%. The overall relapse rate was 13.6%. Arthritis and fever were the most common clinical findings of brucellosis. Wright test is a very sensitive method to detect brucella infection. Public education and control measures should be applied to prevent the zoonotic and human brucellosis.

Acta Medica Iranica 2008; 46(6): 489-494.

Key words: Brucellosis, pediatric infection, clinical features

INTRODUCTION

Brucellosis is a common chronic infectious disease which is caused by aerobic gram negative coccobacilli termed Brucella species (1). This disease is a zoonotic infection that humans are its accidental host with no role in its reservoir. The disease can be transmitted in different ways, mainly by consumption of un-pasteurized milk and cheese (2). The persons who deal with domestic animals and their products, such as shepherds, farmers, veterinarians and butchers are at risk of brucellosis.

According to the report of World Health Organization (WHO), the prevalence of zoonotic and human brucellosis have increased in Mediterranean region, middle east and west Asian countries, as well as some regions of south America and Africa during two recent decades (3). Iran and five other eastern Mediterranean countries have accounted more than 90000 patients with brucellosis (4). Keeping on conventional rearing domestic animals and other factors such as nutrition habits, environmental and personal health and methods of milk preparation have made this disease being endemic in Iran (5).

The clinical manifestations of human brucellosis vary from a subacute clinical disease to a chronic disease. Some of the disease symptoms are fever,

Received: 6 Feb. 2007, Revised: 4 Jun. 2007, Accepted: 7 Sept. 2007

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sweating, anorexia, malaise, weight loss and depression. Arthritis is the most common feature of local brucellosis which often involves knee and hip joints. In addition, neurobrucellosis and endocarditis are serious but uncommon manifestations of the disease (6). Leukopenia, anemia and thrombocytopenia or pancytopenia may be found in this disease (2). Interestingly, a case of thrombocytopenic purpura has been reported as only clinical manifestation of brucellosis (7).

The diagnosis of brucellosis is established by obtaining the microorganism from blood, bone marrow or other tissues. However, it should be considered that culture of brucella requires long-term incubation (1). Recently, the organism could be isolated from patients' synovial fluid in one week, using BACTEC culture system (8). The seroagglutination tests with titers above 1/160 suggest the disease, and the acute brucellosis can be proved using 2-mercaptoethanol (2-ME) test (1).

Treatment of brucellosis cause improvement of signs and symptoms of the disease, decrease its complications and prevent replace and chronic disease. The therapeutic regimen depends on patient's age and underlying conditions. For adults, the antibiotic therapy with doxycycline and rifampin for 45 days or doxycycline for 45 days and streptomycin for two weeks are recommended. Tetracycline should not be prescribed for the children under 8 years old and the pregnant women because of adverse effects on teeth. Therefore, trimethoprim/sulfamethoxazole (co-trimoxazole) is used with rifampin or gentamicin. The relapse rate is less than 8% using these therapeutic regimens (9). In one study, minocycline which is a tetracycline agent was used in children under 8 years old for 3 weeks without findings of dental defects (10).

Brucellosis is a disease which can be treated by proper diagnosis and knowledge of its signs and common clinical findings play major role in disease control. This subject is more significant in children. The aim of this study was to identify common clinical manifestations and laboratory findings of brucellosis in children under 14 years old in Tehran, capital of Iran. This is of interest because there are similar reports from other parts of this country with demographic and epidemiologic characteristics different from those of our region (11-16). Furthermore, the study on childhood brucellosis is limited in Iran and some other aspects of epidemiologic characteristics of brucellosis were defined in current study.

MATERIALS AND METHODS

This retrospective study was performed on 44 pediatric patients ≤ 14 years of age and suffering from brucellosis who were admitted in Pediatric Medical Center Hospital in Tehran, Iran, from March 1988 to February 2001. The patients had been followed for one year. As a tertiary medical center, our department serves a large population who live in Tehran and referring from other cities.

The diagnostic criteria of the disease were positive culture of bone marrow specimen or Wright test (serum agglutination test) with titers > 1:160 and clinical signs compatible with brucellosis. Based on existing prior data of medical documents, the checklists consisted of demographic information of patients, chief complaints, laboratory and clinical findings and type of treatment was completed. Then, the data was retrospectively analyzed. Data were statistically summarized by using the SPSS Version 13.

The protocol for the research project has been approved by Ethics Committee of Tehran, University of Medical Sciences. Also, it confirms the provisions of the Declaration of Helsinki in 1995.

RESULTS

Of 44 patients studied, 29 (65. 9%) were males. The mean age of patients was 7.31 (age range 1.5-12) years. The majority of patients (70.4%) had presented at the first half of year. Out of all, 61% was urbanite and remaining population was living in the rural areas. Only 11% of patients had come from the families of high-risk group, including shepherds, farmers, veterinarians, butchers, *etc*. Positive family history of brucellosis and prior use of un-pasteurized milk and dairy products were reported by 20.4% and 65.9% of patients, respectively.

The most common signs and symptoms were arthralgia/arthritis (79.5%) and fever (77.4%) (Figure 1). The hip and knee joints were involved in 52% of patients, and half of patients had multi-articular involvement. Leukopenia was observed in 14 (31.8%) children, and the remaining patients had normal leukocyte count with no case of leukocytosis. Other hematological findings included anemia and thrombocytopenia in four (9.1%) and 25 (56.8%) patients, respectively. Erythrocyte sedimentation rate (ESR) < 30 mm/hr, in the range of 30-50 mm/hr and > 50 mm/hr were observed in 34.1%, 36.4% and 29.5% of patients, respectively. Fifteen (34%) patients had positive C-reactive protein (CRP). Other biochemical tests such as bilirubin, renal function tests and electrolytes were normal.

For 52.3% of patients, the primary diagnosis was brucellosis at admission time, while 29.5% and 18.2% of patients had been admitted for arthritis and fever of known origin (FUO), respectively. Blood culture had been performed for 20 cases, among which six (30%) positive specimens was reported. Amongst patients with primary diagnosis of FUO, 10 (50%) of 20 cultures of bone marrow was positive for Brucella species. The Wright test was positive in 43 (97.7%) patients, and only one patient had negative Wright test. In 20 (50%) patients, the Combs Wright test was performed and all tests were positive. The 2-ME test was performed for 22 patients which was positive in more than 75% of the cases (Table 1).

Table 1. Laboratory findings in children with brucellosis

Laboratory findings	Number	Percent
Cell blood count (n = 44)		
Anemia	25	56.8
Leukopenia	14	31.8
Thrombocytopenia	4	9.1
ESR (mm/h) (n = 44)		
<30	15	34.1
30-50	16	36.4
>50	13	29.5
CRP (n = 44)		
Positive	15	34
SAT (n = 44)		
Positive	43	97.7
Coombs SAT (n = 20)		
Positive	20	100
2-ME test (n = 22)		
Positive	17	75
Blood culture (n = 20)		
Positive	6	30
Bone marrow culture (n = 20)		
Positive	10	50

Abbreviation: SAT, serum agglutination test (Wright test).

In children under 8 years old, a combination of co-trimoxazole with rifampicin (6-week treatment course) or co-trimoxazole with gentamicin were used for 20 (45.4%) and 10(22.7%) patients, respectively. In remaining patients, antibiotic regimes consisted of different combinations such as doxycycline with rifampicin or co-trimoxazole with streptomycin.

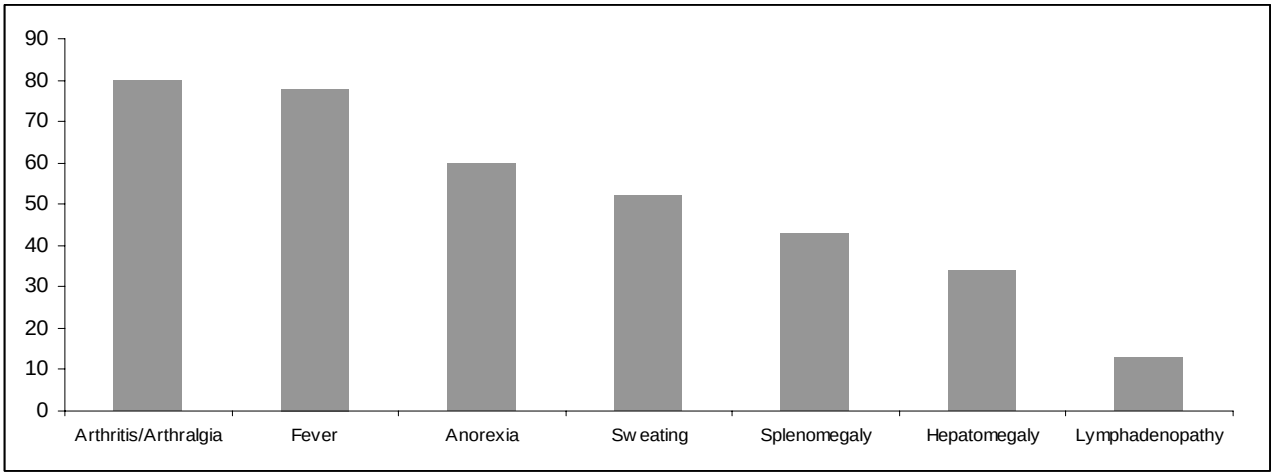

Fig. 1. Symptoms and signs of children with brucellosis.

DISCUSSION

Brucellosis is a disease with profound public health and economical impact. It is more prevalent in developing than in developed countries, especially high-risk groups. Brucellosis in children accounts for 3 to 10% of all reported cases. The main source of infection in children is consumption of un-pasteurized dairy products (1-3).

In current survey of documented brucellosis in children, the male to female proportion was 2:1, in accordance with Shaalan *et al.* study with 115 patients and Almuneef *et al.* study with 64 patients in Saudi Arabia (17, 18). Recently, in a large study on brucellosis patients, Mantur *et al.* have reported that the males were three times as affected as females (13). One of the reasons that the boys are affected more than girls may be the more exposure to the domestic animals. Regarding to age distribution of our patients, seven (16%) patients were under 3 years old and the youngest patient was 18 months old. Consequently, the disease is not uncommon among patients under 3 years of age, and young children with signs suggesting brucellosis should be evaluated for this infectious disease.

In accordance to the studies of Mantur *et al.* and Salari *et al.* (16, 19), many of our patients had consumed un-pasteurized dairy products. Therefore, further public education is required to decrease consumption of un-pasteurized dairy products, and also attention to this point of patient's history can help to diagnosis of the brucellosis.

In accordance with Roushan *et al.* study (20), more than two third of our patients had presented at spring and summer seasons. It may be due to whether fresh dairy products are produced and consumed more frequently or travels are increased to the regions where domestic dairy products are found a lot during these seasons. However, this seasonal prevalence can be applied in principal programs of government to prevent disease incidence.

The most common clinical finding was articular involvement, especially hip, similar to study of Tsolia *et al.* (21). However, fever was more common than arthralgia/arthritis in other similar studies in Iran (12, 13, 19). Splenomegaly and hepatomegaly were slightly common in our patients (43.2% and 34.1%, respectively). In study of Tsolia, splenomegaly and hepatomegaly have been reported in 38% and 28% of the cases, respectively, while Roushan, Elbetagy and Gottesman *et al.* have recorded organomegaly in less cases (25.5%, 6.4% and 22.6%, respectively) (11, 22, 23). However, brucella has predilection for reticuloendothelial system, so involvement of related organs is expected and should be considered in clinical examinations.

In current study, 18% of brucellosis cases had presented with FUO. Therefore, it is recommended that brucellosis being considered and necessary tests performed in evaluation of FUO patients even if no sign of brucellosis exists.

In our patients, white blood cell counts showed that leukocyte count was in the normal range or decreased. Anemia, thrombocytopenia and few cases of pancytopenia were found, but none of children had leukocytosis. The ESR value had no specific pattern. Similarly, Gottesman *et al.* reported that there was no correlation between the ESR value and severity of illness (23). It seems that hematological laboratory findings are nonspecific for diagnosis of brucellosis, as Young has implicated (1, 2). Conversely, serological methods were helpful and positive for diagnosis of brucellosis almost in all patients. In brucellosis, the positive blood culture can be found from 15 to 70% of patients depending on conditions of culture techniques and duration of incubation (2). In our patients, 30% of blood specimens were culture positive, while culture of bone marrow specimen was positive in 10 (50%) patients admitted for FUO. This finding suggests that culture of bone marrow specimen is more sensitive than blood culture to obtain causative organism of the disease. As detection of causative organism of the disease documents the diagnosis of brucellosis, it is necessary not only to perform culture of blood and bone marrow specimens in all patients with suspected brucellosis, but also to preserve the culture of specimen for a long time (at least for 30 days) or to apply BACTEC system if it is possible.

In current study, the majority of patients were treated with two antibiotic regimens: 1) oral co-trimoxazole and rifampin, and 2) co-trimoxazole and

gentamicin. Children under 8 did not received tetracycline agents. However, the relapse rate was remarkable (13.6%). Compliance of patients and their parents for completion of treatment course should also be considered in efficacy of these therapeutic regimens. Recently, Caslio *et al.* have reported that the relapse rate was fewer than 2% with minocycline and rifampin (24). In another study, Miedang *et al.* observed no relapse with combination therapy using three antibiotics for six weeks (25). Also, in Mantur's study, patients had no relapse with combination therapy with three antibiotics for 2 weeks and then following with combination therapy with two antibiotics for 6 weeks (21). However, Roushan *et al.* reported failure of therapy and relapse rate of 10.9% and 4.5% for 6 and 8 weeks therapy with co-trimoxazole plus rifampicin, respectively (26).

In conclusion, it seems that arthritis and fever are the most common clinical findings of brucellosis. Wright test is a very sensitive method to detect Brucella infection. Culture of blood and bone marrow specimens in suspected cases of brucellosis is required to establish the diagnosis. Public education and control measures should be applied to prevent the zoonotic and human infection. Further prospective investigations are required to select an appropriate antibiotic regimens regarding to possible resistance of Brucella species to current antibiotic agents and controversial treatment of brucellosis in children.

Conflict of interests

The authors declare that they have no competing interests.

REFERENCES

1. Young EJ. Brucella species. In: Mandell GL, Bennet JE, Dolin R, editors. Principles practice of infection diseases. 5th edition. New York: Churchill Livingstone; 2000. P. 2387-2391.
2. Young EJ. Brucellosis In: Feigin RD, Cherry JD, Demmler GJ, Kaplan SL, editors. Textbook of pediatric infectious diseases. 5th ed. Philadelphia: Saunders; 2004. P. 1582-1587.
3. [No authors listed]. Brucellosis in 1988 and 1989. Wkly Epidemiol Rec. 1991 Apr 12;66(15):104-106.
4. Abdon A. Brucellosis in the eastern Mediterranean region. Paper presented at the regional conference on emerging infectious disease. Cairo, Egypt 1995 Nov: 26-29.
5. Issa H, Jamal M. Brucellosis in children in south Jordan. East Mediterr Health J. 1999 Sep;5(5):895-902.
6. Schutzie GI, Jacobs RF. Brucellosis In: Behramn RE, Kliegman RM, Jenson HB, editors. Nelson textbook of pediatrics. 17th ed. Philadelphia: Saunders 2004; 939-940.
7. Yalaz M, Arslan MT, Kurugöl Z. Thrombocytopenic purpura as only manifestation of brucellosis in a child. Turk J Pediatr. 2004 Jul-Sep;46(3):265-267.
8. Yagupsky P, Peled N, Press J. Use of BACTEC 9240 blood culture system for detection of Brucella melitensis in synovial fluid. J Clin Microbiol. 2001 Feb;39(2):738-739.
9. Solera J.Treatment of human brucellosis. J Med Liban. 2000 Jul-Aug;48(4):255-263.
10. Cascio A, Di Liberto C, D'Angelo M, Iaria C, Scarlata F, Titone L, Campisi G. No findings of dental defects in children treated with minocycline. Antimicrob Agents Chemother. 2004 Jul;48(7):2739-2741.
11. Roushan MR, Gangi SM, Ahmadi SA. Comparison of the efficacy of two months of treatment with co-trimoxazole plus doxycycline vs. co-trimoxazole plus rifampin in brucellosis. Swiss Med Wkly. 2004 Sep 18;134(37-38):564-568.
12. Hasanjani Roushan MR, Mohraz M, Hajiahmadi M, Ramzani A, Valayati AA. Efficacy of gentamicin plus doxycycline versus streptomycin plus doxycycline in the treatment of brucellosis in humans. Clin Infect Dis. 2006 Apr 15;42(8):1075-1080.
13. Roushan MR, Ahmadi SA, Gangi SM, Janmohammadi N, Amiri MJ. Childhood brucellosis in Babol, Iran. Trop Doct. 2005 Oct;35(4):229-231.
14. Ayatollahi J. Epidemiological, clinical, diagnostic and therapeutic survey of 686 cases of brucellosis. Ann Saudi Med. 2004 Sep-Oct;24(5):398-399.
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 Dec;17(12):904-907.

16. Salari MH, Khalili MB, Hassanpour GR. Selected epidemiological features of human brucellosis in Yazd, Islamic Republic of Iran: 1993-1998. East Mediterr Health J. 2003 Sep-Nov;9(5-6):1054-1060.
17. Shaalan MA, Memish ZA, Mahmoud SA, Alomari A, Khan MY, Almuneef M, Alalola S. Brucellosis in children: clinical observations in 115 cases. Int J Infect Dis. 2002 Sep;6(3):182-186.
18. 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 Feb;15(1):76-80.
19. Mantur BG, Akki AS, Mangalgi SS, Patil SV, Gobbur RH, Peerapur BV. Childhood brucellosis--a microbiological, epidemiological and clinical study. J Trop Pediatr. 2004 Jun;50(3):153-157.
20. Hasanjani Roushan MR, Mohrez M, Smailnejad Gangi SM, Soleimani Amiri MJ, Hajiahmadi M. Epidemiological features and clinical manifestations in 469 adult patients with brucellosis in Babol, Northern Iran. Epidemiol Infect. 2004 Dec; 132(6):1109-1114.
21. Tsolia M, Drakonaki S, Messaritaki A, Farmakakis T, Kostaki M, Tsapra H, Karpathios T. Clinical features, complications and treatment outcome of childhood brucellosis in central Greece. J Infect. 2002 May; 44(4):257-262.
22. Elbeltagy KE. An epidemiological profile of brucellosis in Tabuk Province, Saudi Arabia. East Mediterr Health J. 2001 Jul-Sep;7(4-5):791-798.
23. Gottesman G, Vanunu D, Maayan MC, Lang R, Uziel Y, Sagi H, Wolach B. Childhood brucellosis in Israel. Pediatr Infect Dis J. 1996 Jul;15(7):610-615.
24. Cascio A, Scarlata F, Giordano S, Antinori S, Colomba C, Titone L. Treatment of human brucellosis with rifampin plus minocycline. J Chemother. 2003 Jun; 15(3):248-252.
25. El Miedany YM, El Gaafary M, Baddour M, Ahmed I. Human brucellosis: do we need to revise our therapeutic policy? J Rheumatol. 2003 Dec; 30(12): 2666-2672.
26. 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 Jun;25(6):544-545.