Evaluation of childhood brucellosis in the central Black Sea region

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Brucellosis is a systemic infectious disease that leads to various clinical pictures and is still a significant health problem in Turkey. In this study, 52 pediatric patients diagnosed with brucellosis between January 2008 and December 2013 were examined. Clinical and laboratory findings, response to treatment, prognosis and complications were evaluated. Diagnosis of brucellosis was made based on a clinical picture compatible with the disease, together with standard tube agglutination test (SAT) positivity (1/160 or higer titer) or isolation of *Brucella* spp. in a sterile body fluid culture. The cases comprised 10 females and 42 males. In 75% of cases, there was a history of consumption of unpasteurized milk or dairy products. The most commonly seen symptoms and findings were fever (75%), arthralgia (54%), fatigue (19%), splenomegaly (44%), hepatomegaly (42%) and arthritis (19%). Atypical presentations were seen in one case of epidydymo-orchitis and three cases of bleeding of the nose and gums. In the laboratory examinations, anemia was determined in 56% of cases, leukopenia in 40% and thrombocytopenia in 27%. In blood cultures taken from 41 patients, *Brucella* spp. were isolated in 23 (56.1%). All patients recovered, and sequelae were seen only in a patient with osteoarthritis. In conclusion, although brucellosis leads to many different clinical pictures, a very good response to treatment can be obtained. If effective treatment cannot be implemented in time, the disease may become chronic, and complications and relapses may be encountered. Therefore, early diagnosis and treatment is of great importance.

Key words: brucellosis, childhood, complication.

Brucella strains comprise small, nonmotile, aerobic, gram-negative coccobacilli. *Brucella melitensis*, which is the most invasive and pathogenic species of the four strains, is responsible for the most cases worldwide. The spread of brucellosis, a zoonotic disease, occurs through direct contact with infected animals or consumption of infected animal products. While risk exists for those working with farm animals and for laboratory personnel, the majority of pediatric cases of the disease arise from the consumption of unpasteurized milk or dairy products[1,2].

After infection, the microorganism, which can cause multisystem involvement, proliferates in the regional lymph nodes, passes into the blood and causes systemic infection involving tissue and several organs, primarily the reticuloendothelial system[1]. The main complaints of patients are sudden onset of fever, sweating, fatigue, headache, backache and arthralgia. In endemic countries, the presence of fever of unknown origin is a significant reason to suspect brucellosis[3]. Hepatomegaly and splenomegaly may be found in many cases. Bone and joint involvement are the most frequently seen complications in brucellosis, and hematological, neurological, gastrointestinal and genitourinary system

involvement may also be encountered[1,4].

In this study, a retrospective evaluation was made of the demographic and clinical characteristics, laboratory findings, treatment and complications of 52 pediatric cases with brucellosis.

Material and Methods

In this study, an evaluation was made of 52 patients diagnosed with brucellosis and admitted to the Ondokuz Mayis University Faculty of Medicine Pediatric Hospital for treatment between January 2008 and December 2013. Diagnosis of brucellosis was made based on a standard tube agglutination test (SAT) titer ≥1/160 together with clinical findings such as fever, arthralgia, fatigue and weight loss, or *Brucella* spp. isolation in a sterile body fluid culture. Approval for the study was granted by the local ethics committee.

A record was made of the patient's age, gender, place of residence, season of presentation, contact with animals, consumption of unpasteurized milk and dairy products and presence of similar diseases in the family. According to the duration of symptoms prior to presentation, disease was classified as acute (for symptom duration less than 2 months), subacute (duration between 2 and 12 months) and chronic (duration of more than 1 year)[2]. Evaluation was made in respect of complaints on presentation, physical examination findings, laboratory test results such as complete blood count, liver function test results, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and sterile body fluid cultures.

Anemia, thrombocytopenia and leukopenia were defined as hemoglobin level of < 10 g/dl, leukocyte count of < 4,600/mm^3 and platelet count of <150,000/mm^3, respectively. Blood

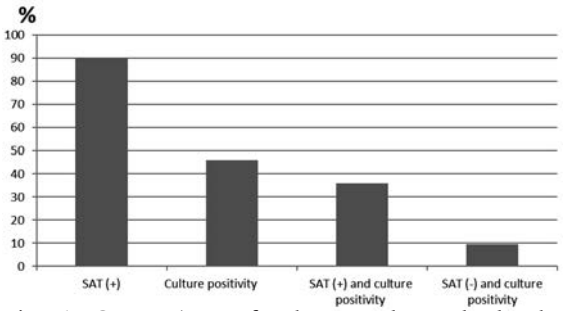

Fig. 1. Comparison of culture and standard tube agglutination titer
SAT: Standard tube agglutination titer

culture samples were sent in BacT/ALERT (bioMerieux, Marcy, France) culture bottles and placed in automatic culture systems. Positive growth was subcultured on blood, eosin methylene blue and chocolate agar mediums.

For children younger than 8 years of age, trimethoprim/sulfamethoxazole+rifampicin was given, and for those older than 8 years of age, doxycycline+rifampicin or doxycycline+aminoglycoside. For cases with osteoarticular involvement, streptomycin or gentamicin was administered for 2 weeks additional to the paired regime. The treatment period was defined as six weeks, but this period was extended in cases with bone involvement[1].

In the statistical evaluation of the study data, SPSS 15.0 software was used. Continuous variables with normal distribution were stated as mean±standard deviation (SD) and others as median (minimum-maximum); frequency data were given as percentages (%).

Results

The study included 52 patients diagnosed with brucellosis. The patients comprised 10 females (19.2%) and 42 males (80.8%), with

Table I. Symptoms and Signs of Brucellosis Cases

Symptoms	n (%)	Signs	n (%)
Fever	39 (75%)	Splenomegaly	23 (44.2%)
Arthralgia	28 (53.8%)	Hepatomegaly	22 (42.3%)
Leg pain	16 (30.8%)	Arthritis	10 (19.2%)
Fatigue	10 (19.2%)	Petechiae	3 (5.7%)
Weight loss	4 (7.7%)	Epydidymo-orchitis	1 (1.9%)
Nosebleed	3 (5.7%)		
Night sweats	2 (3.9%)		

Table II. Laboratory Findings in Brucellosis Cases

Finding	n (%)
Anemia	29 (55.6%)
Leukopenia	21 (40.3%)
Thrombocytopenia	14 (26.9%)
Pancytopenia	11 (21.0%)
Increased CRP	35 (67.3%)
Increased ESR	25 (48.0%)
Increased AST	18 (34.6%)
Increased ALT	14 (26.9%)

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

a mean age of 11 years (range, 2-17 years). The spring months saw the greatest number of patients (18 patients, 34.6%) admitted to the hospital, followed by the summer months (17 patients, 32.7%).

Families of 41 patients (78.8%) worked with livestock. Consumption of unpasteurized milk or dairy products was determined in 39 cases, and in 17 cases (32.7%), there was another case of brucellosis in the family. In 14 patients (26.9%), the animals from which they had consumed milk had a history of miscarriage.

When the duration of symptoms at the time of presentation was examined, 30 patients (57.7%) were defined as acute and 22 patients (42.3%) as subacute. There were no cases defined as chronic brucellosis.

The most commonly encountered symptoms and findings were fever (75%), arthralgia (53.8%), fatigue (19.2%), splenomegaly (44.2%), hepatomegaly (42.3%) and arthritis (19.2%) (Table I). A 14-year old male patient whose father had a history of brucellosis presented with complaints of pain, swelling and redness in the scrotum, and a positive SAT titer of 1/1280 was determined, so brucella epididymo-orchitis was considered in that case. Three cases presented with bleeding of the nose and gums.

In the laboratory tests, anemia was observed in 29 patients (55.6%), with a mean hemoglobin value of 11.7 g/dl (min: 7.2–max: 14.3 g/dl). Leukopenia was determined in 21 patients (40.3%), with a mean white cell count of 5.785±2.399/mm^3 (Tables II-III). Thrombocytopenia was determined in 14 (26.9%) patients, with a mean thrombocyte value of 222.000±109.162 /mm^3. Pancytopenia was observed in 11 (21%) patients. An increased aspartate aminotransferase (AST) level (> 45 U/L) was determined in 18 patients (34.6%), and increased alanine aminotransferase (ALT) (> 40 U/L) in 14 (26.9%). CRP was found to be elevated (> 5mg/L) in 35 patients (68%), and ESR (> 20 mm/h) in 25 (48%).

The serum agglutination test was administered to all patients, and was positive in 47 (90.4%). In the 5 patients (9.6%) with SAT values < 1/160, diagnosis was made from the isolation of *Brucella* spp. in blood and/or joint fluid cultures. In 19 patients (36.5%), both SAT and culture were determined positive (Fig 1). Of the blood cultures taken from 41 patients (78.8%), 23 (56.1%) showed positive results. Of these, 15 (65.2%) were identified as *B. melitensis*. In addition, *B. melitensis* was isolated in joint fluid in 4 patients, 3 of whom also had *B. melitensis* isolated in blood culture.

Twenty-eight patients (58.8%) had complaints of arthralgia. In 12 patients, magnetic resonance imaging (MRI) or computed tomography (CT) was conducted; arthritis was determined in

Table III. Complications in Children Diagnosed with Brucellosis

Complications	n (%)
Hematological system	
Anemia	29 (55.6%)
Thrombocytopenia	14 (26.9%)
Pancytopenia	11 (21.0%)
Skeletal system	
Peripheral monoarthritis	10 (19.2%)
Osteomyelitis	1 (1.9%)
Genitourinary system	
Epididymo-orchitis	1 (1.9%)

10 (19.2%) of these cases (9 hips, 1 knee). One of the cases with hip arthritis had also iliac bone involvement and osteomyelitis. The patient recovered without any sequelae after 6 months of medical treatment. Another patient with hip arthritis, a 16-year old male, was given doxycycline, rifampicin and streptomycin treatment. Movement disability continued in this patient, and surgery was performed. Medical treatment was completed in 6 months. However, complaints of mild restriction in flexion of the hip joint and limping continued. With the exception of this case, all of the patients recovered without sequelae.

Of the total 52 patients, 41 (78.9%) came for follow-up examinations. Eleven patients (21.1%) did not come for regular follow-up. Recovery was observed in all cases except the one patient with hip arthritis mentioned above.

During treatment, nail color change associated with doxycycline was observed on the 40th day of treatment in one patient (1.9%), doxycycline-related esophagitis in one (1.9%), doxycycline-related allergic rash in one (1.9%) and trimethoprim/sulfamethoxazole-related allergic rash in one (1.9%). As the nail color change occurred on the 40th day of treatment, doxycycline was stopped, and at follow-up, the color change was seen to have disappeared. Similarly, the complaints of the patient with esophagitis became evident on the 35th day of treatment, so the medication was terminated, and three days later the complaints had completely resolved. In cases where medication allergy developed, the medication was changed.

Discussion

Brucellosis is a zoonotic disease, which is endemic in developing countries and still seen in rural areas of developed countries as well[5]. It is endemic in Turkey and more often seen in the regions of East and Southeast Anatolia, where farming is more pervasive[2]. The disease affects all age groups. In previous studies of children, it has been found to be seen around the age of 9 years and usually in males[6,7,8]. In our study, the mean age was 11 years and the rate of male cases was 80.8%.

Although the disease may be seen throughout the year, it is generally more prevalent in Turkey in the spring and summer months because of lambing and increased production of cheese[2]. In our study, too, most of the cases presented in the spring months.

Patients may present with a variety of clinical symptoms, fever and arthralgia being the most common, as was seen in the present study. Non-specific findings such as weight loss, night sweats and abdominal pain may often be encountered[1,6,7]. However, there may also be atypical presentations. We saw a 14-year old child who presented only with complaints of scrotal pain and swelling. His father had a diagnosis of brucellosis. We investigated the SAT value and found it to be high; the patient was thus diagnosed as brucella epidydymoorchitis. This is generally seen in young adult males but should be kept in mind in regions where the disease is endemic. Early diagnosis and treatment is important in order to avoid complications such as necrotizing orchitis, oligospermia and azoospermia[9].

Arthritis is a significant issue to be considered in the physical examination. Sometimes brucellosis is diagnosed when patients are investigated for arthritis. Bone and joint involvement has been reported at rates of 7-31% in various studies. Generally there is mono-articular involvement, and, as in the our study, large joints such as the hip and knee are usually involved[6,8,10]. The 19.2% incidence of arthritis found in the present study is consistent with data in the literature. Osteomyelitis, which was detected in one case in our study, is a very rare complication of brucellosis in childhood[10,11].

Hematological findings such as anemia, leukopenia and thrombocytopenia are often seen in brucellosis. Although the pathogenesis is not fully understood, hypersplenism, bone marrow suppression and hemophagocytosis may be responsible. In previous studies, anemia has been reported at rates of 44-55%, leukopenia at 21-33%, thrombocytopenia at 5-26% and pancytopenia at 8-14%[12,13]. In this study, anemia, leukopenia, thrombocytopenia and pancytopenia were seen at rates of 55%, 40%, 26% and 21% respectively. While hematological findings are generally seen at a moderate level, there may sometimes be cases with severe thrombocytopenia, developing pancytopenia and bleeding[14-16]. We found severe thrombocytopenia in three cases (5.7%), who presented with bleeding of the nose and gums,

petechiae and purpura.

Gastrointestinal symptoms such as weight loss, abdominal pain, diarrhea and nausea and vomiting may be seen in brucellosis cases. Diarrhea and abdominal pain may be due to mesenteric lymphadenitis, ulceration of Peyer's patches or inflammation. Hepatosplenomegaly may be seen, and liver enzymes may be increased by 50%. Hepatitis is generally subclinical, and jaundice is rare[6]. In our study, increased liver enzymes were seen in 30% of cases, but clinical hepatitis and jaundice were not observed. Symptoms or findings of the central nervous system, cardiovascular system or respiratory system were also not seen in any patients.

The anamnesis is very important in the diagnosis of brucellosis. It must be asked whether there are other cases of brucellosis in the family, whether the family engages in farming, and whether fresh, unpasteurized cheese has been consumed. Isolation of *Brucella* spp. in sterile samples of body fluids or tissues such as blood, bone marrow or joint fluid is the gold standard in diagnosis[1]. Culture positivity has been reported at rates of 15-44% in previous studies[2,6]. *Brucella* spp. were isolated in 23 (56.1%) of the 41 blood cultures of the cases. In addition, *B. melitensis* was isolated in the joint fluid cultures of 4 patients. Tanır et al.[6] reported culture positivity in 17.8% of cases with brucellosis. The majority of those patients were followed up as outpatients. The cases in the present study were all admitted to the hospital, and blood cultures were taken before treatment, so a higher rate of culture positivity was obtained. Serology is often used in the diagnosis of brucellosis. STA positivity has been determined at a rate of 94% in previous studies[2]. In the current study, STA positivity was found to be 90%, and in the 5 cases with negative SAT, the history was consistent with brucellosis and *Brucella* spp. were isolated from the blood and/or joint fluid cultures.

The aim of treatment is to control the acute disease and prevent complications and relapses[1]. As *Brucella* spp. are intracellular pathogens, the medications used must be effective within the cell as well as long-lasting, and a combined regime is recommended. Trimethoprim/ sulfamethoxazole and rifampicin provide a sufficient concentration within the cell[17]. In our study, depending on the age group, treatment of trimethoprim/sulfamethoxazole+rifampicin or doxycycline+rifampicin was administered for 6 weeks. Due to the potential of bone and dental side effects, doxycycline is not recommended for children below the age of 8 years. We saw doxycycline-related esophagitis in one case, nail color change in one case, allergic skin rash in one case and trimethoprim/ sulfamethoxazole-related skin rash in one case. All of these findings resolved when the medication was terminated.

In conclusion, brucellosis leads to many different clinical pictures, and the findings may be confused with those of several other diseases. However, it generally has a benign course and responds very well to treatment. If effective treatment cannot be implemented in time, the disease may become chronic, and complications and relapses may be encountered. Therefore, early diagnosis and treatment are of great importance. Awareness on the part of the public is of key importance for the management of brucellosis and eradication of the disease.

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