Brucellosis: An underdiagnosed infection in children

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ABSTRACT

Brucellosis, which is believed and categorized as an animal disease, can, surprisingly, be found in humans also. We report a 5-year boy presenting to us with prolonged (5 months) unexplained fever, non-tender discrete lymphadenopathy, and hepatosplenomegaly and finally proved to be a case of brucellosis, which was treated appropriately. Brucellosis should be considered as one of the differential diagnoses causing prolonged fever in children.

Key words: *Human brucellosis, Children, India*

Brucellosis is primarily a disease of animals (zoonosis), but it can be transferred to humans by ingestion of infected/contaminated dairy products [1]. Brucellosis is still a very important public health problem in many countries including Mediterranean areas, parts of South and Central America, Africa, and India [2]. *Brucella melitensis* is possibly the most virulent species to cause human infections all over the world including India, followed by *Brucella abortus* and *Brucella suis* [3,4]. Human brucellosis develops following consumption of unpasteurized, contaminated milk or soft cheese infected with *B. melitensis* [5]. Brucellosis was once thought to be an uncommon or mild disease in children but now recognized as an underdiagnosed disease among persons of all ages [1]. It is characterized by myriad of non-specific symptoms along with complications [6]. Being a multisystem disease with protean presentations, brucellosis can often present as a diagnostic dilemma for clinicians [7]. Here, we discuss a 5-year child, with varied presentations at onset, finally diagnosed to have brucellosis.

CASE REPORT

A 5-year boy was referred to the outpatient department of our tertiary care hospital in Northern India. The child had fever without localization for the past 5 months, which was high grade, remittent, and not associated with chills or rigors. He also had weight loss of 5 kg over the past 5 months coupled with mild occasional cough. Due to the illness, he had frequent school absenteeism for the past 5 months. He did not have a history of rash, arthralgia, night sweats, or contact to a proven case of tuberculosis. His father was a truck driver by occupation, and there was a history of exposure to farm animals, although consumption of raw milk was denied. There was no similar family history in any of the family members.

On physical examination, boy had non-significant, non-tender, generalized lymphadenopathy, mild pallor, firm non-tender hepatomegaly of 5 cm below the right costal margin, and splenomegaly of 3.5 cm below the left costal margin. Respiratory system, cardiovascular system, and central nervous system examinations were normal. For fever, he was treated twice with intravenous third-generation cephalosporin and oral azithromycin, each lasting 7–10 days, considering it a case of typhoid fever by local physicians, without clinical response. Laboratory investigations revealed Hb – 9.4 mg/dl, total leukocyte count 9800/mm^3 (45% lymphocytes), platelet count 320,000/µL, and normal peripheral smear and erythrocyte sedimentation rate of 54 mm/hr. Biochemical parameters were normal. HIV serology, tubercular workup, Widal test, and ANA test were negative. Chest X-ray was non-contributory.

Brucella standard agglutination test (SAT) showed a titer of 2560 IU which decreased to 1298 IU on treatment with 0.05 M 2-mercapto-ethanol (2ME) showing that it was a recent infection. 5-day blood culture in automated BACTEC 9240 (BD Diagnostics, USA) system was sterile, but prolonged incubation showed the growth of *Brucella* species, which was identified by non-motile, non-capsulated Gram-negative coccobacilli. It gave positive reaction with oxidase, catalase, and urease test and produced acid from xylose in oxidative-fermentative medium [8]. On antimicrobial susceptibility testing, it was sensitive to cotrimoxazole, erythromycin, chloramphenicol, ciprofloxacin, and rifampicin. On the basis of these laboratory reports, diagnosis of brucellosis was confirmed.

He was treated with rifampicin at 15 mg/kg/day and trimethoprim-sulfamethoxazole (TMP-SMZ) TMP at 10 mg/kg/day and SMZ at 50 mg/kg/day for 6 weeks. The intensity of fever started decreasing after 1 week, subsiding after 2 weeks of therapy. At follow-up after 8 weeks, hepatomegaly and splenomegaly also reduced. Child gained weight and did not have recurrence of disease at 9 months of follow-up.

DISCUSSION

In India, brucellosis is predominantly an occupational disease occurring among farmers, veterinarians, and abattoir workers [3]. Although brucellosis comes under differential diagnosis of any algorithm of pyrexia of unknown origin, yet the true incidence of human brucellosis is unknown. Seroprevalence studies suggest that human Brucella infection may range between 0.9% and 18.1% among veterinarians and farm attendees. Prolonged fever is usually the most common clinical manifestation of brucellosis, followed by other features such as arthralgia, hepatosplenomegaly, weight loss, malaise, and poor appetite [9]. Literature mentioned arthralgia in 50–60% of children while arthritis is less commonly seen [10]. Our patient had fever, dry cough, and weight loss with hepatosplenomegaly but no arthralgia or arthritis. Only 16% of children are reported to have present with non-tender, discrete lymphadenopathy [9]. Other less common presentations include vasculitis, deep vein thrombosis, nephritis, and meningitis. Ocular manifestations are seen rarely in the form of optic neuritis, uveitis, and papilledema [11]. Common hematologic findings seen are anemia, leukopenia, and thrombocytopenia [12].

Brucellosis rarely figures in the differential diagnosis of a long-standing fever and most of the time child is investigated for enteric fever and tuberculosis [6]. In endemic countries, brucellosis may also be unknowingly treated by rifampicin presumptively started for tuberculosis. Hence, brucellosis should be considered as one of the differential diagnoses of prolonged fever in children. Blood culture remains the gold standard for diagnosis, which is usually positive between 7 and 21 days but may take up to 6 weeks by the conventional method though using the automated system, majority of the isolates grow in 3–5 days [13]. Blood cultures are positive only in 17–50% of cases of brucellosis; bone marrow cultures have the higher yield and can be used in chronic cases. In addition to blood culture, serology for specific antibody detection is an alternative tool for early diagnosis; standard tube agglutination (SAT) is the most widely used method. SAT detects both IgM and IgG antibodies against *Brucella*, and titers >1:160 are suggestive of acute infection. IgG quantification can be done by the treatment of serum with 2-ME, which is more useful after treatment to follow response. Although enzyme-linked immunosorbent assay (ELISA), rose Bengal plate agglutination test, Coombs test, immune-capture agglutination test, latex agglutination test, and lateral flow assays have been used for this purpose. ELISA can detect IgM and IgG separately so can be used to differentiate between acute and chronic phases of brucellosis. Sensitivity of ELISA has been found to be lower (80% IgM and 50% IgG) than that of SAT (95%). Polymerase chain reaction assays have been developed and are found to have superior specificity and sensitivity in detecting both primary infection and relapse after treatment [14].

Treatment of brucellosis mainly consists of various combinations of drugs such as tetracyclines, streptomycin, rifampicin, and cotrimoxazole (TMP-SMX). Treatment is aimed mainly at treating current infection and prevention of subsequent relapses. Various treatment regimens described include streptomycin with doxycycline, rifampicin with doxycycline, and TMP-SMX with streptomycin or rifampicin (in patients where tetracyclines are avoided). Usual treatment duration is for 6 weeks. However, prolonged therapy is indicated in neurobrucellosis (usually 3–6 months). With these combination of drugs, response rate is very good with less chance of future relapse [15,16]. Relapses are usually seen after monotherapy with rifampicin or streptomycin or when compliance is poor. Most relapses are seen within 6 months of discontinuation of therapy.

CONCLUSIONS

Brucellosis should be considered as one of the differential diagnoses of prolonged fever in children. Timely and accurate diagnosis of brucellosis is challenging due to non-specific clinical features and slow growth rate in blood culture.

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