AN INTERESTING CASE OF CHILDHOOD BRUCELLOSIS WITH UNUSUAL FEATURES

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SUMMARY – Brucellosis is a zoonotic infection, which is still a major public health concern worldwide. Common clinical findings are usually nonspecific involving fever, arthralgia, myalgia, weakness and malaise. Since none of the symptoms of brucellosis is pathognomonic, it may have a similar course with various multisystemic diseases. In terms of focal involvement, sacroiliitis is the most common musculoskeletal manifestation in adult patients, while it is quite rare in pediatric patients. Blood culture is the gold standard in the diagnosis of brucellosis. In the absence of culture facilities, the diagnosis traditionally relies on serologic testing with a variety of agglutination tests such as the Rose Bengal test and the serum agglutination test. However, these agglutination tests are accompanied by frequent false negative results such as seen in prozone phenomenon, which may lead to diagnostic delays. In this article we present a rarely encountered pediatric brucellosis patient who had sacroiliitis-spondylitis, which are rarely reported in children, and exhibited prozone phenomenon in agglutination tests.

Key words: *Brucellosis – diagnosis; Child; Prozone phenomenon; Sacroiliitis; Spondylitis*

Introduction

Brucellosis is reported to be the most frequent zoonotic disease worldwide and it is estimated that 500,000 new cases occur annually[1]. Among *Brucella* species, *Brucella melitensis* is mostly implicated as the causative agent of the disease. Brucellosis may mimic various systemic diseases and usually diagnostic delays occur due to the lack of a rapid and precise diagnostic method. Although serum agglutination tests are widely used, when they yield false negative results the diagnosis may be limited. In clinical presentation, brucellosis may cause systemic or focal disease. Systemic involvement may present with nonspecific symptoms such as fever, arthralgia, myalgia and weakness. Focal manifestations are seen most frequently in the musculoskeletal system, and include sacroiliitis in adults and arthritis of the knee in children[2]. Regarding its severe complications, brucellosis must be considered on differential diagnosis in cases with long lasting and unexplained fever, arthralgia and myalgia symptoms. Here we report a case of a 12-year-old child with brucellosis who had interesting features in terms of clinical presentation and laboratory results.

Case Report

A 12-year-old male patient presented with a one-month history of fever, sweating, weakness and pain in the back, hip and right knee. Physical examination revealed mild splenomegaly and tenderness over the sacroiliac joint with movement. On physical examination, his weight was 50 kg (50-75th percentile) and

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Fig. 1. On coronal post-contrast T1 weighted gradient echo image, contrast enhancement is demonstrated on the superior part of the sacroiliac joint and its capsule.

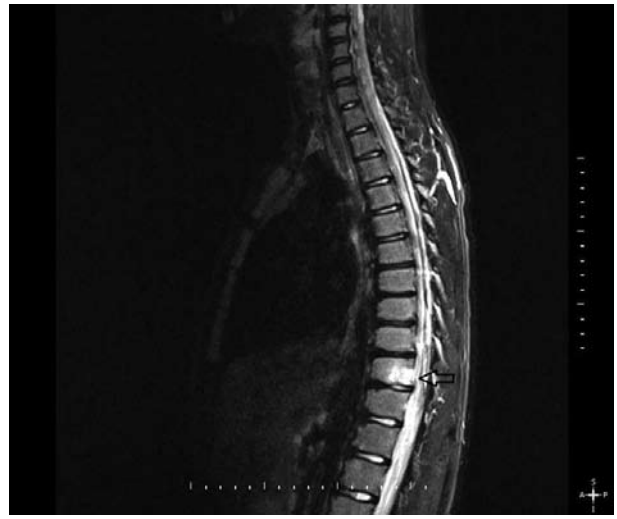

Fig. 2. On sagittal T2 weighted short tau inversion recovery (STIR) image, prominent heterogeneous increase in signal intensity is demonstrated in the posterior aspect of the body of the 10th thoracic vertebra.

height was 158 cm (75-90thpercentile). Body temperature was 38.5 ˚C, heart rate 70/min, blood pressure 110/70 mm Hg and respiratory rate 20/min. Laboratory analysis showed hemoglobin level of 120 g/L and white blood cell count 8.3x10^{9}/L, erythrocyte sedimentation rate was 23 mm/hour and C-reactive protein level was 29 mg/L (upper reference limit: 5 mg/L). Peripheral blood smear examinations showed 38% of polymorphonuclear leukocytes, 55% of lymphocytes and 6% of monocytes without any atypical cell. Renal and liver function tests were within the normal limits. The patient had a positive history of brucellosis cases in his family and of consuming cheese produced by unpasteurized milk. According to these clinical and laboratory findings, with an initial diagnosis of brucellosis, further serologic tests were studied. The Rose-Bengal test was positive, while the *Brucella* standard tube agglutination test was negative. Cardiologic evaluation and echocardiographic investigation that were performed because of the bradycardia episodes seen on the initial days of hospitalization were both normal. Although direct x-rays of vertebral and sacroiliac joints were reported as normal, contrast enhanced magnetic resonance imaging (MRI) revealed spondylitis at the 10th thoracic vertebra and unilateral sacroiliitis (Figs. 1 and 2). Owing to the isolation of *Brucella* spp. in blood culture, agglutination tests were repeated with immunocapture method and yielded positive result at a titer of 1/320. Ultimately, the patient was diagnosed as brucellosis with sacroiliitis and spondylitis. Treatment with streptomycin, rifampicin and doxycycline was started. He received streptomycin for 2 weeks and the other drugs for 12 weeks. During one-year follow up, no complication or relapse occurred.

Discussion

Brucellosis is a zoonotic disease, which is caused by organisms of the genus *Brucella*. Brucellosis is mainly acquired by consumption of unpasteurized dairy products, and rarely by direct contact with infected animals through the skin, by inhalation of infected aerosols or inoculation into the conjunctiva[1,3]. In our case, there was a positive family history for brucellosis and consumption of cheese produced from unpasteurized milk.

Since the signs and symptoms of brucellosis are highly variable and non-pathognomonic, it may have a similar course with various multisystemic diseases. Due to these features, brucellosis is named as a "great imitator, major mimicker or disease of mistakes"[4,5]. The most common symptoms of brucellosis include fever of unknown origin, arthralgia, myalgia, weakness and night sweating[6]. Other symptoms that may be encountered are loss of appetite, fatigue, weight

loss, abdominal pain and headache. Clinical features and history of our patient suggested brucellosis as an initial diagnosis.

Brucellosis may present with long lasting fever alone. Çiftdoğan *et al*. included 92 pediatric patients with fever of unknown origin in their study and reported *Brucella* as the most frequently encountered infectious agent[7].

Focal involvement of brucellosis is mostly related to the osteoarticular system. Other focal involvements may be confined to the central nervous system, respiratory system, hematopoietic system and genitourinary system[3,5,8]. Among musculoskeletal manifestations, sacroiliitis is the most common involvement in adult patients, while arthritis of the knee is the most common involvement in pediatric patients[3,8-10]. Spondylitis in brucellosis mainly affects patients above 40 years of age and occurs as a subacute or chronic infection of lumbar vertebrae[11]. The incidence of spondylitis and sacroiliitis in pediatric patients has been reported to be as low as 0.9%-4.5% and 0.3%-4.5%, respectively[6,10]. Musculoskeletal involvement of our patient manifested as sacroiliitis and spondylitis, both of which are quite rare in childhood.

Table 1. General characteristics of laboratory test methods for the diagnosis of brucellosis[4]

Test	Rose Bengal slide agglutination test	Serum agglutination test (Wright)	Indirect Coombs (antihuman globulin) test	Culture	Microagglutination test	Brucellacapt (immunocapt)
Time	5-10 min	24 h	48 h[a]	3-7 days	24 h	18-24 h
Pros	Rapid	Titration possibility	Detects incomplete, blocking or non-agglutinating immunoglobulins	Gold standard	Uses smaller volumes of serum, can test multiple samples at the time	Single step, can detect blocking antibodies, prevent false positivity and false negativity
Cons	Has false positivity and false negativity	Cumbersome to set up, has false positivity and false negativity	Two steps needed	Time-consuming, hazardous, not sensitive, specialized well-equipped laboratories needed	Cumbersome to set up	
False negativity	Chronic and complicated cases	Chronic and complicated cases, prozone phenomenon		Isolation rate of pathogen is 50%-90%	Chronic and complicated cases	
False positivity	Cross reaction[b]	Cross reaction[b]		No	Cross reaction[b]	
Studied antibody	IgM, IgG	IgA, IgM, IgG	IgG, IgA	-	IgM, IgG	IgA, IgM, IgG

[a] Two-step test; first 24-hour incubation for serum agglutination test, second 24-hour for indirect Coombs test; [b] *Franciella* spp., *Yersinia* spp., *Vibrio* spp., *Echerichia coli* O:157 and lymphomas

Owing to the nonspecific nature of symptoms and since it may be confused with other multisystemic diseases, serologic and microbiologic tests are crucial in the diagnosis of brucellosis. Isolation of *Brucella* spp. from the blood, bone marrow or other tissue fluids is the gold standard for the diagnosis but the isolation rate of this agent is generally low and variable. Therefore, serologic tests are the main tools in the diagnosis of brucellosis in routine practice[4,12]. In our case, in contrast to the initial negative serum agglutination test, the immunocapture agglutination test performed later was found to be positive at a titer of 1/320. False negative serum agglutination test results may be seen in some conditions such as early phase of disease, chronic or complicated course of disease, existence of blocking antibodies or prozone phenomenon (excess of antibodies)[4]. Hence, it is recommended to try further dilutions or different agglutination tests in highly suspect cases with negative initial serum agglutination tests. This approach may prevent delay in the diagnosis and treatment of brucellosis. Table 1 shows the most common tests used in the diagnosis of brucellosis and their characteristics.

Early radiological signs of brucellosis are nonspecific and destructive changes may not be detected on direct radiographs before the third month of the disease, hence, the diagnosis of sacroiliitis or spondylitis may not be achieved. Contrast enhanced MRI is the most frequently advised method for the diagnosis and assessment of musculoskeletal involvement in brucellosis[13]. MRI shows low-to-intermediate signal intensity on T1-weighted images of the intervertebral disc and low signal intensity in the adjacent vertebral bodies. The signals in these areas become hyperintense on T2-weighted MRI sequences[11]. Combined with the clinical features and laboratory results, MR images of our patient were concordant with brucellosis infection.

Trimethoprim/sulfamethoxazole, tetracycline, rifampicin, gentamicin and streptomycin are widely used agents with various dose regimens, durations and combinations in childhood brucellosis. In cases of osteomyelitis, meningitis and endocarditis, a triple combination of tetracycline, rifampicin and aminoglycoside should be used for at least 12 weeks[2,14].

Conclusion

Brucellosis mimics various multisystemic diseases in terms of clinical features, thus posing difficulty during the diagnostic process. Hence, it is recommended to try further agglutination tests in highly suspect cases with negative initial serum agglutination tests. This approach may prevent the need of more invasive procedures and delay in the diagnosis.

References

1. Pappas G, Akritidis N, Bosilkovski M, *et al*. Brucellosis. N Engl J Med. 2005;352:2325-36.
2. Roushan MR, Amiri MJ. Update on childhood brucellosis. Recent Pat Antiinfect Drug Discov. 2013;8:42-6.
3. Doganay M, Aygen B. Human brucellosis: an overview. Int J Infect Dis. 2003;7:173-82.
4. Araj GF. Update on laboratory diagnosis of human brucellosis. Int J Antimicrob Agents. 2010;36 Suppl 1:S12-17.
5. Franco MP, Mulder M, Gilman RH, *et al*. Human brucellosis. Lancet Infect Dis. 2007;7:775-86.
6. Ulug M, Yaman Y, Yapici F, *et al*. Clinical and laboratory features, complications and treatment outcome of brucellosis in childhood and review of the literature. Turk J Pediatr. 2011;53:413-24.
7. 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;11:1037-40.
8. Okur M, Erbey F, Bektas MS, *et al*. Retrospective clinical and laboratory evaluation of children with brucellosis. Pediatr Int. 2012;54:215-8.
9. Kokoglu OF, Hosoglu S, Geyik MF, *et al*. Clinical and laboratory features of brucellosis in two university hospitals in Southeast Turkey. Trop Doct. 2006;36:49-51.
10. Tanir G, Tufekci SB, Tuygun N. Presentation, complications, and treatment outcome of brucellosis in Turkish children. Pediatr Int. 2009;51:114-9.
11. Chelli Bouaziz M, Ladeb MF, Chakroun M, *et al*. Spinal brucellosis: a review. Skeletal Radiol. 2008;37:785-90.
12. Mert A, Ozaras R, Tabak F, *et al*. The sensitivity and specificity of Brucella agglutination tests. Diagn Microbiol Infect Dis. 2003;46:241-3.
13. Harman M, Unal O, Onbasi KT, *et al*. Brucellar spondylodiscitis: MRI diagnosis. Clin Imaging. 2001;25:421-7.
14. BOSILKOVSKI M, DIMZOVA M, GROZDANOVSKI K. Natural history of brucellosis in an endemic region in different time periods. Acta Clin Croat. 2009;48:41-6.

Sažetak

ZANIMLJIV SLUČAJ BRUCELOZE NEOBIČNIH OBILJEŽJA U DJETETA

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Bruceloza je zoonotična infekcija koja još uvijek predstavlja znatan javnozdravstveni problem širom svijeta. Najčešći klinički nalazi obično su nespecifični, a uključuju groznicu, artralgiju, mialgiju, slabost i klonulost. Kako nijedan od simptoma bruceloze nije patognomoničan, tijek ove infekcije može biti sličan raznim multisistemskim bolestima. Prema učestalosti, sakroiliitis je najčešća koštano-mišićna manifestacija u odraslih bolesnika, ali je rijetka u pedijatrijskih bolesnika. Krvna kultura je zlatni standard u dijagnostici bruceloze. Kad oprema za kulturu nije dostupna dijagnostika se tradicionalno oslanja na serološko testiranje pomoću raznih aglutinacijskih testova, kao što su Rose Bengal test i test serumske aglutinacije. Međutim, ovi aglutinacijski testovi praćeni su čestim lažno negativnim rezultatima, primjerice u fenomenu prozone, što pak može odgoditi postavljanje dijagnoze. U ovom članku prikazujemo rijedak slučaj pedijatrijskog bolesnika s brucelozom koji je imao sakroiliitis-spondilitis, što se rijetko nalazi u djece, dok su aglutinacijski testovi pokazali fenomen prozone.

Ključne riječi: *Bruceloza – dijagnostika; Dijete; Fenomen prozone; Sakroiliitis; Spondilitis*