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 sacroilitis-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 annually¹. 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 children². 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
height was 158 cm (75-90th percentile). 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. 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". The most common symptoms of brucellosis include fever of unknown origin, arthralgia, myalgia, weakness and night sweating. 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.

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. 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. Spondylitis in brucellosis mainly affects patients above 40 years of age and occurs as a subacute or chronic infection of lumbar vertebrae. 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. 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**

<table>
<thead>
<tr>
<th>Test</th>
<th>Rose Bengal slide agglutination test</th>
<th>Serum agglutination test (Wright)</th>
<th>Indirect Coombs (anti-human globulin) test</th>
<th>Culture</th>
<th>Microagglutination test</th>
<th>Brucella capt (immunocapt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>5–10 min</td>
<td>24 h</td>
<td>48 h&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3–7 days</td>
<td>24 h</td>
<td>18–24 h</td>
</tr>
<tr>
<td>Pros</td>
<td>Rapid</td>
<td>Titration possibility</td>
<td>Detects incomplete, blocking or non-agglutinating immunoglobulins</td>
<td>Gold standard</td>
<td>Uses smaller volumes of serum, can test multiple samples at the time</td>
<td>Single step, can detect blocking antibodies, prevent false positivity and false negativity</td>
</tr>
<tr>
<td>Cons</td>
<td>Has false positivity and false negativity</td>
<td>Cumbersome to set up, has false positivity and false negativity</td>
<td>Two steps needed</td>
<td>Cumbrous to set up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>False negativity</td>
<td>Chronic and complicated cases</td>
<td>Chronic and complicated cases, prozone phenomenon</td>
<td>Isolation rate of pathogen is 50%-90%</td>
<td>Chronic and complicated cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>False positivity</td>
<td>Cross reaction&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Cross reaction&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No</td>
<td>Cross reaction&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studied antibody</td>
<td>IgM, IgG</td>
<td>IgA, IgM, IgG</td>
<td>IgG, IgA</td>
<td>IgM, IgG</td>
<td>IgA, IgM, IgG</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Two-step test; first 24-hour incubation for serum agglutination test, second 24-hour for indirect Coombs test; <sup>b</sup>*Franciella* spp., *Yersinia* spp., *Vibrio* spp., *Escherichia 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. 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). 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. 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. 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.

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

Sažetak

ZANIMLJIV SLUČAJ BRUCELOZE NEOBIČNIH OBLJEŽJA U DJETETA

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