Case Report / *Olgu Sunumu*

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An Adolescent Norobrusellosis Case

Ergen Nörobruselloz Olgusu

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Abstract

Brucellosis is a common zoonosis in our country. It can involve every system and lead to different clinical pictures. Nervous system involvement occurs in 3-10% of brucellosis patients. Headache is a warning sign for neurobrucellosis. A 15-year-old male patient presented with fever, joint pain, headache and vomiting lasting for about five days. His physical examination was unremarkable except for an increase in the left knee joint circumference. A positive 1/1280 titer was observed in the *Brucella* Wright agglutination test of the patient whose C-reactive protein (CRP) elevation and Rose Bengal test were positive. Lymphocytic pleocytosis, high protein and low glucose were detected in cerebrospinal fluid (CSF). *Brucella* CSF PCR test and CSF agglutination test were negative. *Brucella* spp. grew in CSF culture. The patient's complaints regressed rapidly with doxycycline, rifampicin and cefotaxime treatment, and the patient was discharged to complete the doxycycline and rifampicin treatment in 12 weeks.

Keywords: *Brucella*, brucellosis, meningoencephalitis, neurobrucellosis

Öz

Bruselloz ülkemizde sık görülen bir zoonozdur. Her sistemi tutabilir ve farklı klinik tablolara yol açabilir. Sinir sistemi tutulumu, bruselloz hastalarının %3-10'unda gözlenir. Baş ağrısı, nörobruselloz açısından uyarıcı bir bulgudur. On beş yaşında erkek hasta yaklaşık beş gündür süren ateş, eklem ağrısı, baş ağrısı ve kusma ile başvurdu. Fizik muayenesinde sol diz eklem çevresinde artış dışında özellik yoktu. C-reaktif protein (CRP) değeri yüksek ve Rose Bengal testi pozitif olan hastanın *Brucella* Wright aglütinasyon testinde 1/1280 titrede pozitiflik gözlendi. Beyin omurilik sıvısında (BOS) lenfositik pleositoz, protein yüksekliği ve glukoz düşüklüğü saptandı. *Brucella* BOS PCR testi ve BOS aglütinasyon testi negatif olan hastanın BOS kültüründe *Brucella* spp. üredi. Doksisiklin, rifampisin ve sefotaksim tedavisi ile şikayetleri hızla gerileyen hasta doksisiklin ve rifampisin tedavisi 12 haftaya tamamlanmak üzere taburcu edildi.

Anahtar Kelimeler: Brusella, bruselloz, meningoensefalit, nörobruselloz

Introduction

Brucellosis is a common infectious disease in underdeveloped countries. In Türkiye, it is especially common in Central Anatolia, Eastern Anatolia, and Southeastern Anatolia regions. When the 2017 Türkiye Brucellosis Incidence Map of the General Directorate of Public Health, Department of Zoonotic and Vector-Borne Diseases is analyzed, it is seen that Konya province has an incidence rate above the national average with 24.2% (1). Although brucellosis can be seen in all ages and sexes, it is most common between 15-35 years of age. *Brucella* infection can be transmitted to humans in various ways. It is most commonly transmitted by consumption of raw milk and its products or direct contact with infected animals (2). Animal breeders, veterinarians, slaughterhouse workers, health officers and those working in the meat industry are at risk. It can affect many systems in the body and cause different clinical pictures.

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Neurobrucellosis can be divided into three categories: acute meningitis or meningoencephalitis, chronic peripheral form (radiculopathy) and chronic cranial nervous system infection (meningoencephalitis, myelitis, cerebellar involvement, cranial nerve palsies) (3). The most common neurological pathology caused by neurobrucellosis is behavioral changes with a rate of 60%. In addition, there are 50% meningitis, 35.2% peripheral neuropathies, 19% cranial neuropathies, 17% myelopathies, 16% cerebrovascular complications and 11% seizures (4). The diagnosis of neurobrucellosis is based on the presence of any of the following criteria: suspicious symptoms and signs of neurobrucellosis such as severe and persistent headache, insomnia, confusion, depression, behavioral changes, incontinence, nuchal rigidity and any neurological findings on examination that interfere with the patient's normal activity, isolation of the causative agent from cerebrospinal fluid (CSF) and/or positive anti-*Brucella* antibodies in CSF, presence of lymphocytic pleocytosis, high protein and low glucose in CSF, or presence of cranial magnetic resonance imaging (MRI) or computed tomography (CT) scan findings (5). Culture positivity in patients with *Brucella* meningitis has been reported to be 3% (6). Our case is important to emphasize the clinical findings and treatment of neurobrucellosis which is a rare disease.

Case Report

A 15-year-old male patient was admitted to the district state hospital with fever, back and knee joint pain, headache and vomiting for about five days. The fever was especially high in the evenings. Rose Bengal test was positive. He had similar complaints four months ago, which disappeared spontaneously. The patient, who was a student, had no known risky activities in terms of brucella transmission. On physical examination, temperature was 36.4 °C, pulse rate was 71 beats/minute, respiration was 18 breaths/minute, blood pressure was 110/60 mmHg, consciousness was clear, orientation and cooperation were normal. Meningeal irritation findings were negative and there were no pathologic reflexes. There was a one-centimeter diameter between the left and right knee joints, there was no increase in temperature or redness in the joint. Other system examinations were normal. Laboratory tests revealed a peripheral blood leukocyte count of 4990/mm^3 (61.8% neutrophils), C-reactive protein 12.3 mg/L, erythrocyte sedimentation rate 2 mm/h, and procalcitonin 0.09 microgram/L. Liver and renal function tests were normal. Lumbar puncture (LP) was performed because of unexplained headache, vomiting and tendency to sleep. CSF was turbid, 330/mm^3 neutrophils were observed on unstained direct examination and 110/mm^3 neutrophils were observed on stained direct examination. Gram stain was negative. CSF protein was 228.9 mg/dL and glucose was 24 mg/dL (concurrent blood glucose was 110 mg/dL). Blood and CSF cultures were sent. CSF viral-bacterial meningitis polymerase chain reaction (PCR) panel and *Brucella* CSF PCR were negative. There was no growth in blood culture. *Brucella* tube agglutination in serum was positive at a titer of 1/1280. CSF *Brucella* tube agglutination was negative. On the 7th day of hospitalization, *Brucella* spp. was grown in automated (Biomerieux Bact/Alert 3D) CSF culture. Doxycycline, rifampicin, cefotaxime treatment was started. Echocardiography (ECHO) was normal. Cranial magnetic resonance imaging (MRI) was normal. Headache regressed rapidly. On the 17th day of treatment, fever, maculopapular rash, and pancytopenia were detected. Rifampicin and cefotaxime were discontinued considering that it was due to drug reaction. Treatment was continued with ciprofloxacin and doxycycline. When the patient's rash regressed and fever and neutropenia persisted, all drugs were discontinued and filgrastim was given for three days. In the follow-up, the treatment of the patient whose neutropenia regressed without fever was continued with rifampicin and doxycycline under close observation. The rash did not recur. The cause of the rash was evaluated as drug reaction due to cefotaxime. The patient's parenteral treatment (cefotaxime followed by ciprofloxacin, rifampicin, and doxycycline) was completed for a total of one month, and the treatment was completed for 12 weeks with oral doxycycline and rifampicin. A control LP was not performed because his complaints resolved and no neurologic deficit was observed.

Discussion

Although globally rare, neurobrucellosis is reported to be relatively common in countries endemic for brucellosis. Neurobrucellosis is estimated to account for 0.5% of community acquired CNS infections (3). In different studies evaluating patients with brucellosis in our country, it was concluded that neurobrucellosis cases were found with different frequencies between 2.7% and 17.8% (7). In studies, the most common clinical findings have been reported as 91% fever, followed by 87% headache, 67% meningeal findings, 65% nausea and vomiting, 22% loss of consciousness, 13% focal neurological deficits, 11% papilledema, 11% seizures and 5% behavioral changes (8). When CSF is examined in neurobrucellosis, lymphocytic pleocytosis, increased protein, normal or slightly decreased glucose levels are frequently observed as in our patient.

Brucellosis is diagnosed by isolation of the microorganism from blood, bone marrow, liver, lymph node, CSF, synovial fluid, prostatic fluid samples and/or serology positivity in the presence of clinical findings (9). However, since serologic tests can sometimes give negative results, diagnosis can be challenging as the sensitivity of culture-based methods varies depending on laboratory techniques and the amount of bacteria in the CSF (10). Other diagnostic methods such as CSF metagenomic next generation sequencing (mNGS) and 16s rRNA sequencing technique are also used in the diagnosis of neurobrucellosis (11). However, they are rarely found in endemic areas. In a study conducted in India in 244 brucellosis patients, positivity in blood culture was 15.2%, positivity in CSF culture was 10.5%, SAT (serum agglutination test) positivity was 80.5% in serum, 75.4% in CSF, and Rose Bengal test positivity was 83.3%. In CSF, especially lymphocytic pleocytosis and protein elevation were reported (12). In our patient, a definitive diagnosis was made with growth in automated CSF culture.

The general principle of treatment is combination regimens with antibiotics with good intracellular transmission. In the presence of focal complications such as meningitis, endocarditis, spondylitis, the principles of antibiotic therapy are similar to the treatment of uncomplicated brucellosis, but the duration of treatment should be longer (at least 8-12 weeks) (5). Tetracyclines are the most effective drugs in the treatment of brucellosis, but the risk of relapse is high with monotherapy. Doxycycline is a long-acting tetracycline derivative, lipophilic, penetrates well into tissues and body fluids, and crosses the blood brain barrier well (13). Rifampicin is another option in the treatment of brucellosis due to its in vitro activity, good penetration into macrophages and leukocytes and good penetration into tissues. Synergistic interaction with tetracyclines in vitro (14). Since some third generation cephalosporins reach high concentrations in CSF, they can be added to doxycycline and rifampicin treatment for 2-3 weeks in the initial treatment of neurobrucellosis, but sensitivity tests are recommended (13). In our patient, cefotaxime, doxycycline, and rifampicin combination was preferred as initial treatment. The efficacy of corticosteroids in neurobrucellosis has not been confirmed to date. However, they have been used in clinics such as arachnoiditis, cranial nerve involvement, myelopathy, demyelinating lesions, high intracranial pressure, and optic neuritis/papilledema (15). Since these clinical findings were not present in our patient, it was not preferred.

In conclusion, brucellosis is a systemic disease in which all organ systems can be involved. Neurobrucellosis is one of the most important clinical manifestations and may have permanent neurologic sequelae. Reduction of morbidity is possible with early diagnosis and appropriate treatment. It is critical that brucellosis is well recognized and treated by physicians in endemic areas. Headache should be a warning sign for the presence of meningitis even in the absence of other findings suggestive of meningitis. Our patient was diagnosed with brucellosis despite a normal family history and no risk factors for transmission. Prevention of brucellosis in humans depends on the eradication and control of brucellosis in domestic animals. In this respect, veterinarians and physicians should work in collaboration.

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