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Case Report / Olgu Sunumu

Neurobrucellosis: Two Cases, Two Different Presentation

Nörobruselloz: İki Olgu, İki Farklı Prezentasyon

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Abstract

Brucellosis is an infectious disease seen particularly in developing countries with a high rate of morbidity. It can affect any system in the body and lead to different clinical presentations. The patients presented here draw attention because they were different presentations of rarely encountered central nervous system involvement. Case 1, a 17-year-old male patient was referred to our hospital with symptoms including sudden-onset fever, headache, vomiting, and being unable to speak and walk. On physical examination, the patient had a fever of 37.5 °C, he was lethargic and had no orientation and cooperation. Lumbar puncture was performed. Cerebrospinal fluid (CSF) findings were consistent with purulent meningitis. Case 2, it was learned that a 34-year-old male patient went to a physician two weeks ago due to a decrease in hearing. He was brought to the emergency room because of the deterioration in his time and place orientation and his symptoms of agitation gradually increased after a headache that started in the morning. It was learned from his relatives that similar symptoms happened again about a month ago, but he did not consult a physician because it resolved spontaneously within a few hours and he had been using depression treatment for more than a year. In the physical examination, his temperature was 37.2 °C, the patient was unconscious, his orientation and cooperation were limited. There was no neck stiffness, and Brudzinski's neck phenomenon and Kernig's sign were negative. Both patients were diagnosed as having neurobrucellosis through blood and CSF examinations and they both recovered with appropriate treatment. Here, we report and discuss two patients with neurobrucellosis with different clinical features.

Keywords: *Brucella*, brucellosis, meningoencephalitis, neurobrucellosis

Öz

Bruselloz özellikle gelişmekte olan ülkelerde görülen önemli ölçüde morbiditeye sahip bir enfeksiyon hastalığıdır. Vücutta her sistemi tutabilir ve farklı klinik tablolara yol açabilir. Burada sunulan olgular, nadir görülen santral sinir sistemi tutulumunun farklı prezentasyonları olmaları nedeniyle dikkat çekmiştir. Olgu 1, 17 yaşında erkek hasta ani başlayan ateş, baş ağrısı, kusma, konuşamama ve yürüyememe şikayetleri ile başvurdu. Fizik muayenesinde, ateşi 37,5 °C idi bilinci letarjikti, hastanın oryantasyonu ve kooperasyonu yoktu. Lomber ponksiyon yapıldı. Beyin omurilik sıvısı (BOS) bulguları pürülan menenjit ile uyumlu idi. Olgu 2, 34 yaşında erkek hastanın iki hafta önce duymasında azalma nedeniyle doktora gittiği öğrenildi. Sabah başlayan baş ağrısı ardından zaman ve yer oryantasyonunda bozulma, ajitasyon şikayetlerinin giderek artması üzerine acile getirildi. Benzer şikayetlerin bir ay kadar önce yine olduğu ama birkaç saat içerisinde kendiliğinden gerilediği için doktora başvurulmadığı ve bir yılı aşkın süredir depresyon tedavisi gördüğü de yakınından öğrenildi. Fizik muayenesinde; ateş 37,2 °C idi, hastanın şuuru bulanıktı, oryantasyon ve kooperasyonu kısıtlı idi. Ense sertliği yoktu, Brudzinski ense fenomeni ve Kernig bulgusu negatif idi. Her iki hasta kan ve BOS incelemeleri ile nörobruselloz tanısı alarak uygun tedavi ile iyileşti. Burada, klinik görünüşleri farklı olan iki nörobrusellozlu olgu sunulup tartışıldı.

Anahtar Kelimeler: *Brucella*, bruselloz, meningoensefait, nörobruselloz

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Introduction

Brucellosis is a common infectious disease in underdeveloped countries. It can cause different clinical presentations by affecting many systems in the body. Depression and loss of attention are common symptoms in brucellosis, but direct invasion of the central nervous system (CNS) is seen in less than 5% of the cases (1). The clinical presentations seen in neurobrucellosis include meningitis, encephalitis, meningoencephalitis, myelitis, radiculoneuritis, brain abscess, epidural abscess, granuloma, and demyelinating and meningovascular syndromes (2,3). Our patients are presented to emphasize that neurobrucellosis, which is seen rarely, should be kept in mind, especially in endemic regions because of its different presentations.

Case Reports

Case 1

A 17-year-old male high school student was admitted to the emergency department with symptoms of sudden-onset fever, headache, vomiting, and an inability to speak and walk. It was learned that he spent 2-3 days a week with fever for the last 15 days, had sweated profusely at night, his interest in his surroundings decreased recently, and he was sleepy even during the day. It was learned from his relatives that his family were farmers and that he had reported having headaches for about five months but did not consult a physician because it was relieved by painkillers. The physical examination findings were as follows: body temperature was 37.5 °C, pulse rate was 61/min, respiration rate 20/min, and blood pressure 108/57 mmHg. He was lethargic and he had no orientation or cooperation. Neck stiffness, Brudzinski and Kernig signs were positive. No pathologic findings were found in other system examinations. In his laboratory tests, the peripheral blood leukocyte value was 12,000/mm^3 (56% neutrophil), C-reactive protein (CRP) was 3.2 mg/l, the erythrocyte sedimentation rate (ESR) was 12 mm/h, and there was no abnormal value in other biochemical parameters. No papillary edema was observed in the ophthalmologic examination. There was no bleeding, shift or edema in cranial tomography. A lumbar puncture (LP) was performed. In a cerebrospinal fluid (CSF) direct examination, the leukocyte count was 250/mm^3 (75% neutrophil). The CSF protein level was 154 mg/dl and the glucose level was 2.4 mg/dl (simultaneous blood glucose level was 93 mg/dl). He was admitted to the pediatric ward. Considering meningitis due to brucella, ceftriaxone, doxycycline, and rifampicin was initiated. Samples were sent for blood and CSF cultures. A Brucella Tube Agglutination Test and Rose Bengal test were performed. In the follow-up, on the first day of hospitalization, the patient was bradycardic (46-66/min). His consciousness did not improve. He was referred to an infectious diseases specialist. An examination for tuberculosis and brucellosis was recommended from the CSF sample. Vancomycin was added to the treatment. On the second day of vancomycin treatment, an improvement in consciousness was observed and neck stiffness continued but it was decreased. A wright agglutination test was positive at titers 1/640 in serum and 1/160 in CSF. The current treatments were continued. On the fifth day of his admission, *Brucella* spp. reproduced in the culture. Neurobrucellosis was confirmed as the diagnosis; vancomycin was discontinued and ceftriaxone, doxycycline, and rifampicin treatments were continued. A follow-up LP was performed when the triple therapy was given for one month. In a direct examination of CSF, the leukocyte count was 40/mm^3 and the erythrocyte count was 30/mm^3. The CSF protein level was 119 mg/dl and the glucose level was 25 mg/dl (simultaneous blood glucose level was 81 mg/dl). Improvement was observed in the clinical follow-up, but the response to the current treatment was found to be insufficient, and 3x400 mg trimethoprim-sulfamethoxazole was added to his treatment. The patient, whose general condition and compliance to treatment was good, was discharged on the 38th day of ceftriaxone + doxycycline + rifampicin treatment, on the 9th day of trimethoprim-sulfamethoxazole treatment, with the request of him and his family. At the end of the treatment, there were no symptoms or abnormal physical examination and laboratory findings in the outpatient clinic follow-up. No follow-up LP was performed.

Case 2

A 34-year-old male stockbreeder patient was brought to the emergency room due to a change in consciousness. It was learned that he had had brucellosis one year ago and received treatment for six weeks. It was learnt that he went to the physician two weeks ago because of a sore throat and hearing loss, and cefaclor was initiated. It was learnt that he had headaches that started in the morning, then he became disoriented in time and place, agitated, did not understand what was said, did not obey commands, and made meaningless movements. It was learnt that similar symptoms happened again a month ago, but the patient did not consult a physician because they regressed spontaneously within a few hours and that he was admitted to the emergency department as these symptoms gradually increased. In the physical examination, his body temperature was 37.2 °C, pulse rate was 83/min, respiration rate was 15/min, and blood pressure was 125/66 mmHg. He was unconscious, his orientation and cooperation were limited. There was no neck stiffness. Brudzinski and Kernig signs were negative. He had no pathologic reflex. No pathologic findings were found in other system examinations. In his laboratory test, the leukocyte value in peripheral blood was 8300/mm^3 (88% neutrophil), CRP was below 3 mg/l, the ESR was 2 mm/h. In his biochemical tests, there were no abnormal findings, except for a minimal increase in blood glucose and lactic dehydrogenase (LDH) levels (glucose: 115.6 mg/dl, LDH: 294 mg/dl). LP was performed, leukocyte count was 200/mm^3 (50% neutrophil), protein level was 93 mg/dl, glucose level was 23 mg/dl (simultaneous blood glucose level was 107 mg/dl) in CSF. Samples were sent for blood and CSF cultures and antibody tests. There was no reproduction in the cultures. Wright agglutination test was positive at 1/1280 titer in serum and 1/80 titer in CSF. Triple therapy (ceftriaxone + doxycycline + rifampicin) was started. Before the completion of the 24 hours of treatment, the patient was conscious, his orientation and cooperation were normal. The symptoms of headache and hearing loss continued. He did not have fever. In the audiologic examination performed on the 5th day of the treatment, mixed-type hearing loss was detected. Pure-tone average (PTO) was 50 decibels in the left ear and 47 decibels in the right ear. Temporal tomography performed to investigate the etiology of the mixed-type hearing loss was evaluated as normal. Ten days after the first test, the hearing test was repeated. A 5-decibel improvement was detected in the right ear (PTO: 50/42 dB). Methylprednisolone (1mg/

kg) was added to the treatment with the recommendation of the otorhinolaryngology department on the 29th day of antibacterial treatment because the improvement did not continue in the second visit. The patient, whose general condition was good and who wanted to be discharged, was discharged after three months of treatment with the combination of trimethoprim-sulfamethoxazole + doxycycline + rifampicin. No improvement was found in the hearing test performed during the outpatient clinic follow-up on the 43rd day of antibacterial treatment and the 13th day of corticosteroid treatment (PTO: 52/43 dB). It was concluded that there was no response to steroid treatment and that he had permanent hearing loss of retrocochlear type.

Discussion

Brucella-type bacteria are facultative intracellular microorganisms that live in macrophages. They use different mechanisms to avoid the host defense, penetrate the host cell, and alter intracellular functioning. With these mechanisms, they escape from being killed in lysosomes, change the intracellular environment, and live in the cell for a long time and replicate. In addition, it is thought that lipopolysaccharides surrounding the bacteria prevent cell death (apoptosis) by suppressing the natural and specific immunity in the host (2,4). The chronic nature of the disease, complications, and relapses are attributed to this feature of the bacterium (2,4,5,6).

Although brucellosis manifests with many different symptoms in the acute and chronic stages, CNS involvement has been reported at a rate of 2-10% in different series (7). In various studies evaluating patients with brucellosis in our country, it has been concluded that the frequency of patients with neurobrucellosis ranges between 2.7% and 17.8% (8). As in many Mediterranean coastal countries, brucellosis is seen as endemic in our country (9). The region we are in is also a region where patients with brucellosis are common in our country (9,10). When the "2017 Map of Brucellosis Incidence of Turkey" of the Department of Zoonotic and Vector Diseases of the Public Health General Directorate is examined, it is seen that the incidence in our city is above the national average with 24.2% (10). In a study we conducted in our center, among 75 patients with brucellosis followed up over eight years, the most common complications were found to be hematologic complications and one patient had confusion (11). In another study, symptoms of the CNS such as diplopia, unsteady gait, and forgetfulness were the least frequent among the 70 patients followed up, as in our series (12).

When CSF is examined in neurobrucellosis, lymphocytic pleocytosis, increased protein levels, and normal or slightly decreased glucose levels are often observed. *Brucella*-type bacteria can be isolated in blood and/or CSF culture (2). In a case series, it was reported that the rate of isolation of an agent from the CSF of patients diagnosed as having CNS involvement varied between 0% and 30% (9). Because neutrophilic pleocytosis and very low glucose levels were unexpected findings in neurobrucellosis in our first patient, although serology was shown positive, treatment revision could not be performed, and vancomycin treatment was discontinued per the result of the culture. This patient also highlights the importance of anamnesis in the diagnosis of diseases. Triple treatment may not be considered in the empirical selection because purulent meningitis is considered primarily when only CSF findings are taken into account.

Combination regimens with antibiotics with good intracellular transmission is the general principle of treatment in brucellosis. In the presence of focal complications such as meningitis, endocarditis, and spondylitis, antibiotic treatment principles are similar to uncomplicated brucellosis treatment, but the treatment duration should be longer (at least 8-12 weeks). Tetracyclines are the most effective drugs in the treatment of brucellosis. Doxycycline is preferred because it crosses the blood-brain barrier better than tetracycline (1). Because some third-generation cephalosporins reach high concentrations in the 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 (2). We preferred a ceftriaxone + doxycycline + rifampicin combination as the initial treatment in our patients. Trimethoprim-sulfamethoxazole was added to the treatment in the first patient because there was not enough improvement in the first-month follow-up LP, ceftriaxone was discontinued after nine days of the quadruple treatment, and the total treatment period was three months. In the other patient, after using the combination of ceftriaxone + doxycycline + rifampicin for one month, trimethoprim-sulfamethoxazole + doxycycline + rifampicin was given for three months.

Hearing loss due to brucellosis is found at rates that cannot be underestimated (13,14,15,16). Although conductive-type loss can also be observed, sensorineural-type loss is reported to be more common (13). When the relationship between the age of the patients and hearing loss is examined, it is seen that hearing loss is more common over the age of 30 years. This is attributed to the chronic course of the disease and longer contact with the pathogen (13,17). Our patient with hearing loss was aged 34 years and the hearing loss was thought to be due to brucellosis because it could not be explained by any other reason. In addition, it was learned that our patient had been treated for brucellosis a year before. In 10-15% of patients with brucellosis, relapse can be seen after antimicrobial treatment. Relapse brucellosis is defined as the recurrence of similar symptoms and signs within 1 year after the completion of brucellosis treatment (2). Relapses are mostly not attributed to antibiotic resistance, but inadequate and incorrect antibiotic use (2,18). In our patient, we could not reach the treatment information of the previous attack. However, relapse rates exceeding 15% have been reported with the frequently preferred use of the doxycycline-rifampicin combination (19).

Although corticosteroids are recommended in neurobrucellosis, their effectiveness has not been proven because there are no controlled studies (2). In our clinic, in a patient with brucellosis without neurologic findings, rifampicin + doxycycline treatment, as well as corticosteroids were used for acute-onset hearing loss and a complete recovery was observed. We found no documents suggesting that corticosteroids were recommended for the treatment of hearing loss in the course of brucellosis. In the literature, steroids are used in patients with neurobrucellosis with optic neuropathy, papilledema, cranial nerve involvement, arachnoiditis or clinical deterioration despite antibacterial therapy (20). However, either the direct spread of the bacteria to the CNS or autoimmune mechanisms related to their toxins are held responsible for neurobrucellosis. Benefiting from corticosteroids in hearing loss in neurobrucellosis may be due to this second mechanism. Still, the most effective approach known to prevent

permanent hearing loss is to initiate antibacterial therapy as soon as possible (16,17).

As a result, brucellosis is a systemic disease in which all organ systems in the body can be involved. Neurobrucellosis is one of the most important clinical presentations and may cause permanent neurologic sequelae. The reduction of morbidity is possible with early diagnosis and appropriate treatment. Brucellosis must be recognized and treated by physicians in regions where it is endemic.

Ethics

Informed Consent: Informed consents were obtained in writing from the father of the first patient from the second patient himself for the publication of this case report.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.Z.A., M.A., M.Y., E.N.T., O.K., G.R.Y., Design: F.Z.A., Data Collection or Processing: M.Y., Analysis or Interpretation: F.Z.A., M.A., E.N.T., O.K., G.R.Y., Literature Search: F.Z.A., M.Y., Writing: F.Z.A., M.A., E.N.T., O.K., G.R.Y.

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