

Neurobrucellosis as a rare complication of brucellosis: three pediatric case reports

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Summary

Brucellosis is a major worldwide zoonosis. The disease is endemic in developing countries, particularly in the Mediterranean basin. Brucellosis is frequently seen in Eastern and South-Eastern Anatolia regions in Turkey. Around 18 000 new cases are reported annually in Turkey. Any organ or system of the body can be involved. Brucellosis is an infection due to *Brucella* species and is characterized by acute febrile illness, sweating, weakness, and headache. Involvement of the central nervous system is rare in brucellosis. *Brucella* is continuing to be an important health problem especially who live in the countryside. The clinicians usually rule out neurobrucellosis in the differential diagnosis of brucellosis. The three neurobrucellosis cases presented in this paper referred with various non-specific symptoms. Only the first patient was found to have hydrocephalus on CT imaging, while the CT images of the other patients were normal. The second case had a history of consumption of fresh herby cheese, however the other cases had no such history. These three patients were found to have recovered without sequela during their long term follow up. The aim of this presentation is to draw attention to the importance of neurobrucellosis especially in endemic regions including our country. (*Turk Arch Ped* 2012; 47: 216-219)

Key words: Brucellosis, neurobrucellosis, zoonosis

Introduction

Brucellosis is a zoonotic infectious disease characterized with non-specific signs and symptoms which can involve many organ systems in the body. The main ways of transmission include oral transmission by infected milk and dairy products, inspiration of barn dust in the environment where infected animals live or cutaneous way as a result of contact with infected animals or animal products (1). Brucellosis is a multi-system disease which can involve many

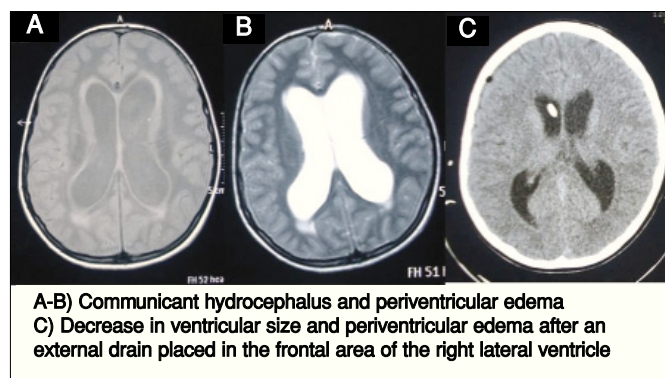
different clinical presentations and complications. Neurobrucellosis occurs in only 1.7-10% of the patients with brucellosis and is one of the complications caused by involvement of the central nervous system (1). In children, neurobrucellosis usually occurs as meningitis and meningoencephalitis (2). The diagnosis of neurobrucellosis is generally made by history, clinical findings and serology or culture results (3). In this article, 3 cases of neurobrucellosis who presented with many different clinical pictures and symptoms were presented.

Case 1

A ten-year old female patient was brought to our Emergency Pediatric Unit by her family because of complaints including fever, headache, nausea, vomiting, somnolence, weight loss, weakness, urinary incontinence and night sweats. The mother stated that she had no appetite and lost weight in the last two weeks. It was learned that she had fever for the last three days and her body temperature increased to 39 °C especially at night and chills and shivering accompanied fever. She had headache and urinary incontinence for the last three days and she had no such complaints before. There was no pathology in her personal history. Her psychomotor development was found to be normal. When she was brought to our emergency unit her body temperature was found to be 38.5 °C (axillary), her heart rate was found to be 106/min (rhythmic) and her blood pressure was found to be 100/60 mmHg. On physical examination, she had a pale and dehydrated appearance. Her eyes were sunken. She had moderate dehydration. Her lung sounds and cardiovascular system examination were found to be normal. No pathology was found on abdominal examination. Neurological examination revealed somnolence, agitation, nuchal rigidity, isochoric pupils and positive direct and indirect light reflex. No loss of strength was found in the upper and lower extremities bilaterally. Deep tendon reflexes were decreased and there was no pathological reflex. Ophthalmological examination revealed stage 1 papilledema. Cranial computerized tomography (CT) revealed communicant hydrocephalus which caused enlargement of the third and lateral ventricles with prominent temporal areas (Picture 1). Laboratory findings were as follows: Hb: 9.8 mg/dL, Htc: 30%, erythrocyte sedimentation rate: 40 mm/h, CRP: 24, leucocytes: 3700/mm³ (70% lymphocyte), hepatic and renal functions tests: normal. Lumbar puncture findings: increased pressure in CSF, cloudy appearance, pandy (++) , leucocytes: 455/mm³ (36% segmented, 64% lymphocyte), protein: 148mg/dL, glucose: 17 mg (simultaneous serum glucose: 74 mg/dL), CSF culture: *Brucella* spp. positive. The same agent was grown in hemoculture. *Brucella* microagglutinin test was found to be positive (1/1380), Eliza IgG and IgM were found to be positive. Gruber Widal test was found to be negative. Wright and Rose Bengal tests were found to be positive. A diagnosis of neurobrucellosis was made, neurosurgery department was consulted and ventricular drainage was performed. After 10 days of drainage the catheter was removed. V-P shunt was not needed, since hydrocephalus did not develop again in the follow-up after catheter removal. 15 mg/kg/day rifampicin and 5 mg/kg/day doxycycline were administered for 6 weeks and 5 mg/kg/day gentamycin was administered for 10 days. Additionally, steroid treatment was administered for 4 days. Repeated CSF culture was found to be negative. The ventricular catheter was removed on the 10th day when hydrocephalus findings regressed. At the end of the treatment period which lasted for 6 weeks blood and CSF cultures became negative. When the laboratory findings were normalized, the patient was discharged in a healthy status.

Case 2

A 15-year-old male patient was brought to our Pediatric Emergency Unit by his father with complaints including fever, somnolence, blurred consciousness, malaise, weight loss and meaningless and unconscious speech. There was no special finding in his personal history. In his history, it was learned that he had fever for three weeks and therefore used different antibiotics and antipyretics the names of which they did not remember. Sometimes vomiting and joint pain accompanied fever during this period. In the last two days, he could not recognize his relatives and spoke meaningless words. When the history was deepened, it was learned that fresh herby cheese was consumed frequently and freshly at home. On physical examination, his general status was poor, his consciousness was blurred and he was not cooperated. Nuchal rigidity and meningeal irritation findings (Kernig and Brudzinski) were found to be positive. On abdominal examination, the spleen was palpable at 3 cm below the left costal margin. Laboratory findings were as follows: leucocytes: 2200/mm³, platelets: 56000/mm³, Hb:12,5 mg/dL, Hct: 37%, ALT: 186 IU/mL, AST: 202 IU/mL. *Brucella* tube agglutination was 1/160 positive in serum and negative in cerebrospinal fluid. CSF findings were as follows: cell number: 75/mm³, protein: 221 mg/dL, glucose: 62 mg/dL (simultaneous blood glucose 88 mg/dL), Cl: 101 mmol/l. No agent could be found on Gram and Ehrlich-Ziehl-Neelsen staining of CSF. *Brucella* spp. were grown in CSF culture. The same agent was grown in hemoculture. Cranial CT was evaluated to be normal. There was no mass effect or edema. After a diagnosis of brucellosis was made with clinical and CSF findings, all family members were investigated in terms of brucellosis and no other case was found. Doxycycline, streptomycin and ceftriaxon treatment was started in the patient in whom rifampicin could not be started, since hepatic enzymes were found to be high. On the 10th day of treatment, streptomycin was stopped and treatment was continued with the other drugs up to 2 months. At the end of treatment, there was no sequela in the patient and hepatic enzymes returned to normal values.



Picture 1. Communicant hydrocephalus

Case 3

A 15-year-old male patient was presented with complaints including fever, malaise, joint pain and abdominal swelling which started 2 weeks ago. In another hospital, his hepatic enzymes were found to be high and urinary urobilinogen was found to be (++++), so he was referred to another center with a prediagnosis of hepatitis for further investigation and treatment. Considering sinusitis antibiotic treatment was given to the patient who had high fever and severe headache and whose acute phase reactants were found to be high. However, his headache became more severe, vomiting started and fever increased with shivering and the patient was brought to our Pediatric Emergency Unit by his family.

On physical examination of the patient who was in the third day of antibiotic treatment, the consciousness was open, the patient was cooperated and had a weak and pale appearance, meningeal irritation findings were negative, diffuse arthralgia and myalgia were present mostly in the extremities. Abdominal examination was normal. No pathology was found on the examination of the other systems. Cranial CT was evaluated to be normal. No mass effect or edema was found. Lumbar puncture was performed in the patient in whom the focus of fever could not be found. CSF findings were as follows: leucocytes 15-20/mm³ (40%PNL, 60% lymphocyte), other biochemical tests were within normal limits. CSF sample was sent for culture. Considering the patient's clinical findings and history the patient was internalized in the ward with a diagnosis of bacterial meningitis with partial response to treatment and bacteremia. 100 mg/kg/day ceftriaxon was started. Since fever persisted in the 24th hour of treatment, 60 mg/kg/day vancomycin was added. Afterwards, the patient's general status was observed to improve rapidly and fever was dropped. As it was planned to complete the treatment in two weeks in the patient whose general status and body temperature were normal, it was learned that gram negative coccobacilli (*brucella* spp) were grown in CSF. Hemoculture was found to be negative. Ceftriaxon treatment was extended to 3 weeks and doxycycline and rifampicin were added. It was planned to give rifampicin for 15 days after ceftriaxon treatment to prevent recurrence in the long term. Wright agglutination test with Coombs was found to be 1/640 positive in the blood. Findings of CSF obtained in the first week of treatment were as follows: 14/mm³ erythrocytes, 15/mm³ leucocytes, protein: 46, glucose: 45 mg/dL (simultaneous blood glucose: 81 mg/dL). Ceftriaxon was extended to three weeks and the patient was discharged by starting streptomycin treatment. In the follow-up, Wright agglutination test was observed to be reduced to 1/80 in the 8th month of treatment. After 9 months of treatment Wright agglutination test was found to be negative. No finding of recurrence was found in the follow-up visits performed 12 months after the end of treatment.

Discussion

Brucella are gram-negative, immobile, aerobic, intracellular coccobacilli. The bacteriae which enter the body firstly go into the reticuloendothelial system, grow here and extend to many organs and systems (4).

Brucellosis is a zoonotic infection which usually has a insidious course, has predominantly non-specific clinical findings and may lead to various complications due to organ involvement. In brucellosis which is a systemic disease, the central nervous system may be involved. In Turkey, 18000 new brucellosis cases are reported each year. The frequency of seropositive cases ranges between 2.6% to 14.4% depending on the geographical distribution, but neurobrucellosis as a complication is observed rarely in children (5,6). Cases of neurobrucellosis can present with non-specific findings (7,8). Neurobrucellosis has been reported to present with mainly meningitis and meningoencephalitis and also other findings including brain abscess, cerebellar ataxia, myelitis, radiculitis and cranial or peripheral nerve paralysis (7,9,10).

The disease is contaminated to humans by urine, feces, saliva and blood of animals and unpasteurized products (milk, cheese, inadequately cooked meat etc.) (1). Recent findings have shown that contamination may also occur by sexual contact and breastfeeding as well as inhalation of aerosols in the laboratory or home (1). In our second patient, there was a history of consumption of fresh herby cheese.

In the childhood, neurological complications of brucellosis are observed rarely (5). In different studies performed in Turkey, the frequency of neurological complications of brucellosis has been found to be 1.7-10% (5,6,9,11). In studies performed outside Turkey, the frequency of neurological complications of brucellosis has been reported to be 2-6.5% (12,13).

The diagnosis in neurobrucellosis can be made by a positive bacterial CSF culture, presence of *Brucella* spp. antibodies in CSF and abnormal CSF findings (more than 10 cells, decrease in CSF glucose, increase in CSF protein) (14). The positivity of *Brucella* agglutination test with Coombs in CSF has been proposed to be very valuable in the diagnosis (14,15). No cell may be present in CSF and normal glucose and protein levels in CSF have been reported (7,9). Although CTs of patients with a diagnosis of neurobrucellosis are normal, brain abscess, enlargement and atrophy of lateral ventricles have been reported rarely (7,8,16). Therefore, association of imaging with clinical findings has been recommended. Hydrocephalus was found in brain CT of our first patient and a V-P shunt was placed by performing surgical treatment in addition to medical treatment. Brain CTs of the second patient were found to be normal. In all of our three patients, *brucella* spp. were grown in CSF and a definite diagnosis was made. However, neurobrucellosis was not considered initially in our third patient and *Brucella* treatment was added when *brucella* was grown in CSF later. In two of our patients, *brucella* spp. were grown in hemoculture. Hemoculture was negative in our third patient.

In children, prognosis is generally good in neurobrucellosis, if treatment is started appropriately and without delay (7). Since *Brucella* is an intracellular infectious agent which can involve various systems with a high recurrence rate, antibiotics with high intracellular penetration should be selected in treatment of Brucellosis. However, triple antibiotherapy is recommended in neurobrucellosis and brucella endocarditis (1). There is no ideal antibiotic regime or period in childhood neurobrucellosis treatment (17). To prevent recurrences dual or triple drugs including rifampicin, trimethoprim-sulphametoxazol, doxycycline (if the patient is older than 8 years) have been recommended to be administered in combination with aminoglycosides including especially streptomycin or gentamicin. Recurrence in Brucellosis may occur in an early period like 2-3 months or 2 years later. It may occur as a result of a viral infection, trauma or another similar cause. We also preferred to use triple drug treatment and we did not give rifampicin to our second patient, since the hepatic enzymes were high. Although the benefit of steroids has not been shown definitely, they may be used to decrease brain edema and eliminate adhesions (18).

If similar signs and symptoms recur in one year after treatment, administration of the previous drugs in combination and triple drug treatment or extending the treatment time to more than 6 weeks may be considered, though there is no definite treatment regime (19). Despite all studies, the most appropriate treatment time and method is not clear in recurrence, chronic brucellosis and complicated brucellosis cases and further multi-center studies should be performed on this subject. In this way, it may be thought that mortality and morbidity related to brucellosis will decrease.

Although neurobrucellosis occurs rarely, it is a severe disease involving the central and peripheral nervous system and may lead to permanent sequelae despite treatment. As a sequela of neurobrucellosis neurosensorial hearing deficit, meningovascular complications (mycotic aneurism, ischemic stroke, subarachnoid hemorrhage), Gullian-Barre syndrome, intracranial abscess, diabetes insipidus, cerebral venous thrombosis and subdural bleeding may develop (20). However, this disease is usually not considered in the differential diagnosis. In fact, the risk of occurrence of brucellosis is high in our country where animal breeding is widespread and food inspection is inadequate. Especially patients with fever and neurological findings should be evaluated well enough and history of each patient should be taken carefully. These three cases were presented to emphasize that neurobrucellosis can lead to persistent fever and non-specific neurological symptoms also in childhood.

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