Acute meningoencephalitis due to Brucella: case report and review of neurobrucellosis in children

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SUMMARY: Türel Ö, Şanlı K, Hatipoğlu N, Aydoğmuş Ç, Hatipoğlu H, Şiraneci R. Acute meningoencephalitis due to Brucella: case report and review of neurobrucellosis in children. Turk J Pediatr 2010; 52: 426-429.

The involvement of the central nervous system (CNS) in brucellosis is rare and has a broad range of presentations. Subacute and chronic meningoencephalitis are described as the most common neurologic manifestations. We report a six-year-old boy with culture-proven neurobrucellosis who presented with an acute picture of meningoencephalitis. Cerebrospinal fluid (CSF) analysis revealed pleocytosis with slight elevation of protein. The agglutination test titer was elevated in serum and Brucella spp. were isolated from both blood and CSF. He was treated with trimethoprim-sulfamethoxazole plus rifampin and streptomycin. His clinical and laboratory features improved with specific antibiotic therapy and no sequela was observed in the short-term follow-up.

Due to protean clinical features, unfamiliarity with the disease can delay the diagnosis in children who are not occupationally exposed. In endemic areas, neurobrucellosis should be considered in the evaluation of patients with unexplained neurologic symptoms.

Key words: brucellosis, children, neurobrucellosis, treatment.

Brucellosis is enzootic in many parts of the world, notably the Mediterranean basin, Arabian peninsula, the Indian subcontinent, and parts of Mexico and South America[1]. Brucellosis is an infection of domestic and wild animals that is transmissible to humans. Acute brucellosis is a systemic illness involving multiple organs or organ systems[2]. Neurobrucellosis comprises a variety of complications including meningoencephalitis, myelitis and myelopathies, peripheral and cranial neuropathies, and psychiatric manifestations[3]. Direct invasion of the central nervous system (CNS) is a rare occurrence and is present in less than 2% of cases[4,5]. Doxycycline in combination with rifampin and trimethoprim-sulfamethoxazole (TMP-SMX) has been used for neurobrucellosis[3-5].

In this report, a case with brucella meningoencephalitis is described and neurobrucellosis in Turkey is reviewed.

Case Report

A six-year-old boy was referred to our hospital because of generalized tonic-clonic convulsions. He had been complaining of fever and headache for five days and was given oral antibiotics, which were ineffective. The boy was the 12th child of the family, with normal psychomotor development and no remarkable prenatal or neonatal event. The family lived in a rural part of Turkey.

On arrival to our hospital, the patient was febrile and stuporous, and nuchal rigidity without significant localizing neurologic changes was observed. Blood cell counts, liver function tests, serum electrolytes, and erythrocyte sedimentation rate were all within normal limits. Chest X-ray was also normal. Ophthalmologic examination delineated normal funduscopy. Lumbar puncture was performed for cerebrospinal fluid (CSF) analysis and culture. CSF examination revealed 187 leukocytes/mm^3, with mononuclear predominance,

glucose 28 mg/dl, and protein 66 mg/dl. Intravenous ceftriaxone and acyclovir were initiated for suspected bacterial meningitis or herpes encephalitis pending culture results and polymerase chain reaction (PCR) for herpes simplex virus type 1 (HSV1) in CSF. Neuroimaging was unremarkable.

On the second day of follow-up, gram-negative coccobacilli were identified in blood and CSF cultures. A presumptive identification of "possible Brucella species" was made due to growth characteristics. The Rose-Bengal test was performed and produced a positive result. Serum agglutination test (SAT) was also positive at a 1/320 titer. Tuberculin skin test was nonreactive and HSV1 PCR in CSF was negative. Acyclovir was discontinued and three antibiotics were added to ceftriaxone: daily TMP-SMX 10/50 mg/kg, rifampin 15 mg/kg, and streptomycin 20 mg/kg.

The patient's mental status improved on the third day of hospitalization and convulsions did not recur. His fever had resolved after the first week of antibiotherapy. On repeated CSF examination, glucose and protein levels normalized, cell count decreased, and culture remained sterile. After three weeks of therapy, he was discharged with clinically satisfactory improvement and oral TMP-SMX and rifampin were ordered to be continued. In the 2nd month of therapy, he was readmitted because of generalized convulsion. On admission, his neurological examination was completely normal and no further convulsions were observed during his stay in the hospital. Cranial neuroimaging studies were repeated, showing no major pathology but increased signal intensity in the left hippocampal regions on T2 flair sequence, which was reported as nonspecific, transient post-convulsive changes by neuroradiology. A repeated CSF examination revealed no leukocytes, glucose 48 mg/dl, and protein 20 mg/L and it remained sterile. SAT in blood and CSF were negative. His treatment was completed to four months and no neurological sequela was observed in the short-term follow-up.

Discussion

Brucellosis remains an important health problem in Turkey. The incidence of brucellosis, reported to be 14% between 1991-2000, had increased to 25.67/100,000 in 2004[6]. It has also been reported that the prevalence of seropositivity among the Turkish population varies from 3-14%[7,8].

Consumption of raw milk and milk products and to a lesser extent contact with infected animals or their waste material are the main routes of infection[9,10]. In the present case, consumption of unpasteurized soft cheese was the route of transmission.

Brucellosis infrequently involves the nervous system but the consequences of neurobrucellosis can be severe[12]. Case series from Turkey show incidences of neurologic complications of brucellosis to range between 6.6 and 17.8%[13,14]. In children, even a lower incidence, <1- 2.2%, is reported[15,16].

Clinical manifestations of neurobrucellosis vary widely, including acute or chronic meningoencephalitis, polyradiculopathy and behavioral disturbances[17]. Symptoms and signs can develop at any stage during the acute or chronic stage but neurologic symptoms are the presenting complaint only on rare occasions[18-20]. In a report of 13 adult patients with neurobrucellosis from Ankara, 77% had chronic presentations[14]. However, neurobrucellosis in children was usually reported to have an acute presentation[21]. Our patient had complaints of only five days' duration.

A definitive diagnosis of brucellosis is established by recovery of Brucella species from blood, bone marrow or other tissues, but this is rarely possible in neurobrucellosis. Most of the cases are diagnosed by positive serology accompanying abnormal clinical and CSF findings[3,4,15]. For unclear reasons, <50% of patients with documented brucellar meningitis will have meningeal signs or symptoms[12]. Our patient had stiff neck at presentation. Analysis of the CSF in brucellar meningitis reveals elevated protein, normal or reduced glucose and a lymphocyte pleocytosis[3-5]. Our patient's clinical features and CSF findings were consistent with acute meningoencephalitis. The rate of isolation of bacteria from the blood in brucellosis is reported to be 15%-70%[10]. However, in neurobrucellosis, bacteria are isolated from the CSF in less than <20% of cases[22]. One of the reasons for this low rate of isolation is the growth characteristics of the bacteria. Brucella are small fastidious microorganisms

and growth *in vitro* is fairly slow. Isolation may require prolonged incubation, so when brucellosis is suspected, cultures should not be discarded before a minimum of 28 days[2]. In our experience, blood and CSF specimens were inoculated on to a blood culture media: BACTEC 9240 (Becton Dickinson, USA). After two days of incubation, bacterial growth was detected on both blood and CSF cultures. A sample was taken from the blood culture bottle from which bacteria was recovered and it was inoculated again to chocolate agar, blood agar and EMB (eosin methylene blue) agar (Oxoid, England), and incubated in a medium containing 5-10% CO_2 at 37ºC for 24 hours for subculturing. Growth was obtained in chocolate agar as minute, round, translucent colonies. Faintly staining coccobacilli were detected in gram-stained smears. They were catalase- and oxidase-positive. A presumptive identification of "possible Brucella species" was made, since the patient had a compatible history (ingestion of unpasteurized milk products). The Rose-Bengal test was also positive. To confirm our diagnosis, we sent a recovered sample to another reference laboratory and the growing bacteria were identified as Brucella spp. SAT, the most commonly used test, can detect antibodies against *B. abortus, B. suis*, and *B. melitensis*[2,12]. Most authorities consider a blood agglutination titer of 1/160 or higher as evidence of active brucellosis in a symptomatic patient[23,24]. The SAT was found to be positive at 1/320 in our patient.

Neurobrucellosis therapy should be a combination of antibrucellar antibiotics such as doxycycline, rifampin and TMP-SMX for 4-6 months[2,12,21]. Although streptomycin or gentamycin is recommended for the first 14 days of therapy, there is a concern since aminoglycosides do not penetrate well into the CSF. In adult studies from Turkey, neurobrucellosis cases were reported to be treated successfully with a combination of doxycycline, rifampin and ceftriaxone[13,14]. Since our patient was younger than eight years, we treated him with TMP-SMX and rifampin for four months. Streptomycin and ceftriaxone were also added during the first 14 days.

Treatment of meningitis usually reverses most neurologic deficits, although some patients have permanent sequelae, particularly if myelopathy is present[3,20]. Our patient responded well to treatment but he had a second convulsive attack in the second month of his therapy. Neurology consultation was normal according to his cranial radioimaging studies. In the short-term follow-up (6 months), no neurodevelopmental delay was observed.

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