An unusual case of neurobrucellosis presenting as demyelination disorder

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Brucellosis is a public health problem in most countries in the Mediterranean. Involvement of the central nervous system is seen in 4-13% of patients with brucellosis. A 13-year-old girl was admitted because of gait disturbance, diplopia, and dizziness. Her complaints began about 1.5 years ago. The second symptomatic episode repeated about three months ago and the third two months ago. In total, attacks repeated 3 times over 1.5 years. The magnetic resonance imaging (MRI) and the clinical features mimicked multiple sclerosis. The patient was given pulse steroid treatments. After steroid treatment, her gait disturbance and diplopia improved over the short term. Following positive developments, her symptoms recurred. The tests were repeated; the MRI showed increasingly high signal abnormalities, and Brucella melitensis was grown in cerebrospinal fluid. The patient was started on an oral combination of rifampin, doxycycline, and ciprofloxacin. MRI findings improved markedly after nine months of treatment. Although neurobrucellosis is associated rarely with demyelination in adults, this finding has not been reported previously in children or adolescents. Additionally, this case is the first in terms of involvement of the corpus callosum in neurobrucellosis. In this article, we present an unusual case of neurobrucellosis.

Key words: neurobrucellosis, demyelination, multiple sclerosis, corpus callosum involvement, neurologic sequelae, white matter.

Brucellosis is considered to be the most widespread zoonosis in the world. It is a public health problem in most countries in the Mediterranean basin, including Turkey, Balkans, Middle East, and South America. Brucella melitensis is still the most common organism in these regions[1]. According to the Turkish Ministry of Health, 6,793 people were hospitalized due to brucellosis in 2004 and the resultant mortality was 3%[2]. Involvement of the central nervous system is seen in 4-13% of patients with brucellosis[3].

Neurobrucellosis may present with meningitis, meningoencephalitis, myelitis, polyradiculoneuritis, and cranial nerve involvement[4-6]. Neurobrucellosis is due to the direct effect of the organism in the acute forms of the disease, while on the other hand, the bacillus may remain in the cell and lead to subacute and chronic manifestations[6]. Although neurobrucellosis is associated rarely with demyelination in adults, this finding has not been reported previously in children or adolescents. In this article, we present an unusual case of neurobrucellosis.

Case Report

A 13-year-old girl was admitted because of gait disturbance, diplopia, and dizziness. Her complaints began about 1.5 years ago, with weakness in her upper and lower extremities. The left side of her face and tongue were numb. Sensorial seizures were considered as a possible cause and the patient was put on valproic acid. Occasional complaints continued. In the last three months before the patient was referred to our center, she was hospitalized in another center due to fever, right leg weakness, gait

disturbance, and right hip pain. The patient was started on an antibiotic. Her complaints improved during the hospitalization period; however, they recurred two months later, and she was referred to our center for further examination.

In the patient's history, there was no consumption of raw milk, ingestion of fresh cheese, or weight gain or loss. She lived in the city. On admission, the patient's vital signs were stable. Her body temperature was normal. The meningeal irritation signs were negative, and she had no lymphadenomegaly or organomegaly. The patient's neurological examination showed the muscle strength of the upper extremities to be 5/5, of the lower extremities 3/5, and a sensory level at thoracal level 10 (no abdominal skin reflexes, symmetric sensory loss present below the umbilicus). Deep tendon reflexes were absent on the lower extremities, and the plantar reflexes were found to be extensor. Cranial magnetic resonance imaging (MRI) showed bilateral high signal abnormalities in the bilateral frontoparietal, cortical, subcortical, and periventricular white matter, and almost all of the corpus callosum on T2-weighted and FLAIR sequences (Fig. 1). Spinal MRI was normal. There was no gadolinium enhancement on the MRI (Fig. 1). The laboratory work-up including complete blood count, erythrocyte sedimentation rate, C-reactive protein, blood biochemistry tests, and collagen disease screening were within normal limits. The MR angiography and EEG were normal.

Visual evoked potential latencies (left) were delayed in response. Unilateral optic neuritis was present upon consultation with the Ophthalmology Department. Cerebrospinal fluid (CSF) analysis revealed: glucose 21 mg/dl, protein 229 mg/dl, red blood cells 50/mm^3, and white blood cells 0/mm^3 (traumatic lumbar puncture). The oligoclonal band was positive, but the immunoglobulin (Ig)G index was normal. The CSF viral markers (including herpes), cultures for bacteria, and gram stain were unremarkable. Two attacks were experienced, more than a month apart, each of which lasted for 24 hours or more; the demyelinating lesions including callosal, cortical, juxtacortical, and periventricular white matter in the cranial MRI, unilateral optic neuritis, and a positive oligoclonal band supported multiple sclerosis. The patient was given pulse steroid treatments. After steroid treatment, her muscle strength improved, up to 4/5, and she had sensory recovery. She was discharged with a prescription for oral prednisolone 2 mg/kg and sodium valproate.

Three days after her discharge she had generalized tonic-clonic seizures. The EEG (routine, sleep) was normal. Carbamazepine was added. However, she had diplopia (abducens nerve palsy), gait disturbance, and three more generalized tonic-clonic seizures. The tests were repeated; the cranial MRI showed increasingly high signal abnormalities (Fig. 2a), and the CSF analysis revealed: glucose levels 10 mg/dl, protein 274 mg/dl, and white blood cells 150/mm^3 (lymphocytes 80%, neutrophils 20%). The Wright agglutination test for brucellosis in the serum was positive at a titer of 1:320. The diagnosis of neurobrucellosis was made, and the patient was started on an oral combination of rifampin, doxycycline, and ciprofloxacin. After 14 days, *B. melitensis* was grown in CSF. MRI findings improved markedly after nine months of treatment (Fig. 2b). She was eventually diplegic, able to walk unassisted for 5-6 meters, with a muscle strength of 5/5 in upper extremities and 4/5 in lower extremities, had hyperactive deep tendon reflexes on the lower extremities, and extensor plantar reflexes.

Discussion

Neurological involvement in brucellosis is rare. The previously reported rate of CNS involvement in the pediatric age group is 0.8%[7]. This rate was reported as slightly higher (1-2.2%) in our country[8,9]. Al-Deeb et al.[4] described five patterns of CNS involvement in brucellosis: meningoencephalitis, meningovascular involvement, CNS demyelination, peripheral neuropathy, and increased intracranial pressure. CNS demyelination or involvement of the white matter is the rarest form of neurobrucellosis[4].

Although the reasons and the exact nature of white matter involvement remain unknown, autoimmune mechanisms have been widely implicated. Cytotoxic T-cells play a key role in the immune response against Brucella microorganisms. Extensive inflammation, which ensues as a result of persistent stimulation of cytotoxic T-cells by bacteria in the CNS,

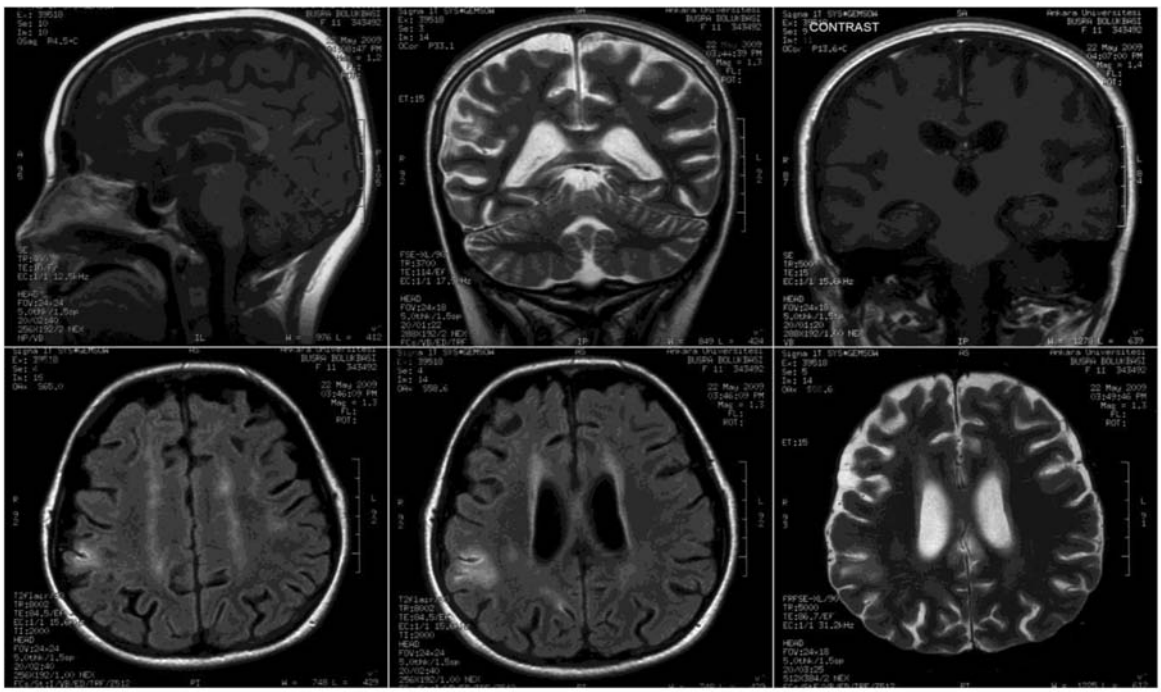

Fig. 1. Magnetic resonance imaging (MRI) findings at admission.

results in marked activation of microglia. The immunological process that follows in the presence of reactive astrogliosis is responsible for the white matter involvement[3]. Early treatment is essential to prevent the progression of this destructive process. Culture growth rates for Brucella may be as low as 25%, which underlines the importance of serologic tests. Initial negative culture results led to a delay in treatment in our patient[10]. It may have been more appropriate if we had utilized serological tests to arrive at an earlier diagnosis.

Three types of imaging abnormalities may be seen in neurobrucellosis: inflammation, white matter changes, and vascular injury. White matter involvement seen in neurobrucellosis may mimic other inflammatory or infectious diseases, such as multiple sclerosis, acute disseminated encephalomyelitis, or Lyme disease[1]. In 1963, Fincham et al.[5] postulated that changes in the white matter seen in neurobrucellosis are sequelae of demyelination, a finding that was confirmed by subsequent histopathological studies. Marconi et al.[11] presented autopsy evidence of demyelination similar to multiple sclerosis lesions in a patient with neurobrucellosis. Similar white matter abnormalities have been described in other patients from the Arabian Peninsula[12]. However, involvement of the corpus callosum has not been reported before[12]. Furthermore, all previous reports of white matter involvement have been in adult cases, making our case presentation unique.

The best treatment of neurobrucellosis remains a controversial topic, with very few guidelines on the most appropriate duration of treatment[13]. Recent reports recommend use of a regimen combining three or four antibiotics[10]. Among the tetracyclines, doxycycline is the drug of choice for neurobrucellosis due to its better tissue and CNS penetrance and longer half-life. Rifampicin and cotrimoxazole also show good penetration into the CSF. Ciprofloxacin combined with other antibiotics has been shown to be as effective as a standard regimen of doxycycline and rifampicin[10]. In neurobrucellosis, treatment should be maintained until clinical symptoms resolve and CSF findings improve.

Clinical features (unilateral optic neuritis and a positive oligoclonal band on CSF) and findings on MRI (demyelinating lesions in the callosal, cortical, juxtacortical, and periventricular white matter) in our patient were highly suggestive of a demyelinating disorder. Despite an early favorable response

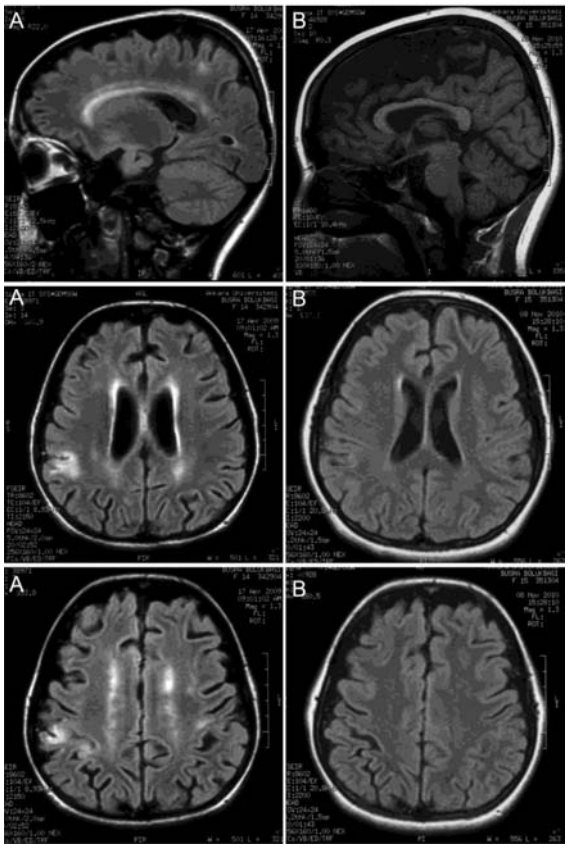

Fig. 2. Magnetic resonance imaging (MRI) findings: a. After recurrence of symptoms, and b. After treatment.

to pulse steroid treatment, her symptoms recurred, with a repeat MRI showing an increase in high signal abnormalities. Combination antibiotic treatment with rifampin, doxycycline, and ciprofloxacin was commenced after the second culture result returned positive for Brucella, following an initial negative result. Marked clinical and radiological improvement was observed by the end of a nine-month treatment course. However, delay in treatment due to a late diagnosis resulted in permanent neurological sequelae.

A diagnosis of neurobrucellosis was made more than a year and half after her symptoms began, and this delay resulted in complications. Early diagnosis and prompt initiation of appropriate treatment are of great importance in preventing the complications of neurobrucellosis. Since brucellosis in an endemic zoonotic disease in Turkey, neurobrucellosis should be considered in the differential diagnosis of patients presenting with a demyelinating disorder.

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