NEUROBRUCELLOSIS AS AN EXCEPTIONAL CAUSE OF TRANSIENT ISCHEMIC ATTACKS

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**SUMMARY**

Incidence of neurologic complications in systemic brucellosis has been reported as 2-10%. Neurobrucellosis (NB) can mimic many central and peripheral nervous system disorders including transient ischemic attacks (TIA), and ischemic or hemorrhagic stroke.

We report a series of four cases presented with TIA or ischemic stroke as the predominant manifestation of NB. Three of the patients were 20-28 years of age, and one patient was 53 years old. They did not possess any stroke risk factors except for smoking. They all used to consume pasteurized milk or its products. Two patients had systemic brucellosis in the past and received antibiotic treatment. All of the patients had systemic symptoms such as headache, fatigue, anorexia, nausea and vomiting, weight loss or lumbar pain, but no systemic signs of brucellosis accompanying ischemic cerebral symptoms. The second most frequent neurological sign was sensorineural hearing loss. Other causes of TIA including cardiac embolism, hypercoagulability, vascular malformations, systemic vasculitis, and infective endocarditis were excluded. NB was diagnosed with serological tests or cultures for Brucella in CSF. All patients were treated with trimethoprim-sulfamethoxazole, doxycycline and rifampicin for at least six months. None of them had any further TIA after the initiation of the treatment.

NB should always be sought in young patients with TIA or ischemic stroke, especially if they have no risk factors for stroke and live in an endemic area for brucellosis, even if they do not have other systemic signs of brucellosis.

**Key Words:** Transient Ischemic Attack, Ischemic Stroke, Brucellosis

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Brucellosis is still a common health problem in some Middle Eastern and Mediterranean countries, although it has been almost eradicated in many developed countries. Nervous system involvement occurs approximately in 2-10% of the patients infected with brucella (1-4).

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Neurobrucellosis (NB) may develop at any stage in the evolution of the disease and may involve several areas of the central and peripheral nervous system. Therefore, NB has widely variable manifestations, including meningoencephalitis, myelitis, radiculitis, neuritis, spinal cord compression and demyelinating or vascular diseases of the central nervous system (CNS), or any combination of these disorders (1-9). The majority of patients exhibit symptoms that fit into more than one category.

The most typical presentation of CNS involvement in brucellosis is chronic meningoencephalitis with mononuclear pleocytosis, low glucose and increased protein concentrations in the cerebrospinal fluid (CSF) (1). Uncommon clinical presentations of NB such as migraine, parkinsonism, optic neuritis, chronic intracranial hypertension, and epilepsy were described (8,10-15). Brucellar meningitis may also behave as an exclusively neurologic disease, mimicking vascular accidents or neurological diseases that are frequently paroxysmal and recurrent (16). Here we report a series comprising four cases with brucellar meningitis as an exceptional cause of transient ischemic attacks (TIA) and ischemic stroke.

Case Reports

Case 1: A 24-year-old woman was admitted with repeated episodes of right hemiparesis, hypoesthesia and dysphasia that were lasting at most an hour. She had experienced eight similar episodes in the last month. The patient was also complaining of having lumbar pain, headache, nausea and vomiting, anorexia and weight loss for the last six months. Her lumbar pain had been attributed to sacroilitis previously. Physical examination was normal. The neurological examination during the last episode revealed motor dysphasia, right hemiparesis, and hypoesthesia, abolished abdominal skin reflex and plantar reflex on the right side. Between these episodes, the neurological examination was completely normal.

Laboratory examinations revealed mildly increased liver enzymes and erythrocyte sedimentation rate (ESR) of 24 mm/hour. Blood counts, prothrombin time (PTT), activated partial thromboplastin time (aPTT), fibrinogen, antithrombin III (AT III), protein C, protein S, activated protein C resistance (aPCR), and antiphospholipid antibodies were within the normal ranges. Immunologic markers including immunoglobulins, C3, C4, crioglobulin, and antinuclear antibodies were negative. No abnormal finding was observed on the plain x-ray of the chest. Cranial computerized tomography (CCT) was normal, but magnetic resonance imaging (MRI) showed a small linear lesion with increased intensity on T2 weighted images (WI) and decreased intensity on T1 WI localized in the posterior insular cortex. Magnetic resonance angiography (MRA) and four-vessel digital subtraction angiography (DSA) of the brain were unremarkable. Transthoracic (TTE) and transeosophageal echocardiography (TEE) showed no abnormality to be the cause of cardioembolism.

Since she used to consume fresh cheese made of cow’s milk and has sacroilitis, brucellosis was considered in the differential diagnosis. Brucella agglutination and Coombs’ tests in blood were both positive in a titer of 1/160. Brucella Rose-Bengal and Ig M (2-mercaptoethanol) were also positive in blood. Cerebrospinal fluid (CSF) appeared clear with an opening pressure of 45cm water. CSF results were shown on the Table 1&2. CSF cultures yielded Brucella melitensis and antibiogram showed susceptibility to rifampicin and doxycycline.

Brucellar meningitis with TIA was diagnosed and treatment with trimethoprim 160 mg/sulfamethoxazole 800mg (TMP-SMZ) three times a day, doxycycline 200 mg/day and rifampicin 900 mg/day was started. In the forth month of the therapy, CSF analysis was repeated. There was no abnormality in CSF examinations except for the positive Coombs’ tests. The patient remained free of TIA since the beginning of the treatment.
A 20-year-old man presented with repeated transient episodes of right hemiplegia and motor aphasia. He had had three similar episodes in the last six months that relieved in a few hours. He was examined by a psychiatrist therefore and treated with antidepressant agents and electroconvulsive therapy. He has been also complaining of having fatigue, nausea, lumbar pain, and a hearing loss in both ears for one year. His physical examination was normal and neurological examination revealed sensorineural hearing loss in the right ear. Audiogram was consistent with bilateral sensorineural hearing loss predominantly in the right ear.

Blood chemistry, blood count, coagulation profile, and hematologic tests for hypercoagulability were normal, and immunologic markers were negative. ESR was 41 mm/hour. CCT showed a focal hypodense lesion with 8mm diameter in the right temporal lobe next to the sylvian fissure. MRI of brain revealed a lesion with increased intensity on T2 WI in the right temporal lobe. Duplex ultrasound of the carotid arteries, TTE and TEE were unremarkable. Brucella agglutination and complement fixation tests in blood were positive in a titer of 1/40 and 1/20, respectively. CSF results were compatible with NB (Table 1&2). Lyme screen, polymerase chain reaction (PCR) for Mycobacterium

<table>
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<th>Leukocyte (N:&lt;10/mm3)</th>
<th>120</th>
<th>48</th>
<th>50</th>
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<tr>
<td>Total protein (15-45 mg/dl)</td>
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<td>77</td>
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<tr>
<td>Albumin (15-40 mg/dl)</td>
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<td>86</td>
<td>84</td>
<td>43</td>
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<tr>
<td>CSF/blood glucose (mg/dl)</td>
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<td>13/91</td>
<td>3/72</td>
<td>26/75</td>
</tr>
<tr>
<td>Ig G (3.3-6.1 mg/dl)</td>
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<td>16.2</td>
<td>13.9</td>
<td>15</td>
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<tr>
<td>Ig A (0.00-0.60 mg/dl)</td>
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<td>2.1</td>
<td>3.64</td>
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<tr>
<td>Ig M (0-1.3 mg/dl)</td>
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<td>1.0</td>
<td>0.6</td>
<td>1.2</td>
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<tr>
<td>Ig G index (0.2-0.50)</td>
<td>0.45</td>
<td>0.60</td>
<td>0.64</td>
<td>2.15</td>
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NE: not evaluated, pathologic results are shown in bold.

<table>
<thead>
<tr>
<th>B. agglutination test (blood)</th>
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<th>1/40</th>
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<th>1/80</th>
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<td>1/20</td>
<td>1/40</td>
<td>1/20</td>
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<tr>
<td>Coombs’ test (CSF)</td>
<td>_</td>
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<td>1/160</td>
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<tr>
<td>Rose-Bengal test (CSF)</td>
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<td>_</td>
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<td>_</td>
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<tr>
<td>Ig M (2-ME) (CSF)</td>
<td>_</td>
<td>_</td>
<td>+</td>
<td>_</td>
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<td>CSF culture</td>
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</table>

NE: not evaluated, pathologic results are shown in bold.
tuberculosis and CSF cultures for brucella and bacteria were negative. The patient was placed on TMP-SMZ three times a day, doxycycline 200 mg/day and rifampicin 900 mg/day.

CSF examination repeated in the forth month of the therapy was not significantly different from the one performed prior to the treatment. However, oligoclonal band was not observed at this admission. Brucella agglutination, Coombs’ and Rose-Bengal tests in CSF remained positive. His sensorineural hearing loss was still remaining in the second year of the treatment, but transient episodes of right hemiparesis and aphasia disappeared after a short time of the treatment.

**Case 3:** A 53-year-old man was admitted with multiple transient episodes of hemiparesis, hypoesthesia and speech disorder improving in an hour and progressive hearing loss in both ears for six months. The last attack that occurred four days before his admission was characterized with nausea-vomiting, tetraparesis and speech arrest, and disappeared in a few hours. He has been complaining of having continuous headache that was not completely responsive to analgesic drugs. He was diagnosed to have brucellosis two years ago and treated with doxycycline 200 mg/day and rifampicin 600 mg/day for three months. He was consulted in the Ear-Nose-Throat Clinics for several times but the progressive hearing loss in his both ears could not be explained. He had no vascular risk factors except for smoking. He was using aspirin 300 mg/day regularly since his first transient ischemic attack.

His physical examination was normal and the neurological examination between the attacks revealed bilateral sensorineural hearing loss and Hoffmann and palmomental reflexes bilaterally. Audiogram showed intermediate sensorineural loss bilaterally. Blood chemistry, blood counts, urine analysis, chest radiography and electrocardiography were normal. ESR was 4 mm/hour. Coagulation profile and all hematologic tests for hypercoagulability were normal. TTE, TEE, duplex ultrasound of the carotid and vertebral arteries, and cerebral DSA were unremarkable. CSF analysis was showed on Table 1&2. Lyme screen, PCR for Mycobacterium tuberculosis and CSF cultures for brucella and bacteria were negative. MRI of brain showed bilateral gadolinium enhancement of trigeminal nerves in cisterns segment, and facial and vestibulocochlear nerves in cavernous segment. Besides, bilateral subcortical lesions in periventricular white matter with increased intensity on T2 WI were observed.

Transient ischemic attack due to brucellosis was diagnosed, and the treatment of TMP-SMZ three times a day, doxycycline 200 mg/day and rifampicin 900 mg/day was started. In the second week of the therapy, rifampicin was discontinued due to resistant nausea-vomiting, hiccup and elevation of hepatic enzymes. Other two drugs were also stopped a few days later, since his complaints did not relieve and hepatic and renal function tests impaired gradually. After the improvement of blood chemistry and the relief of his complaints, TMP-SMZ was restarted. Blood chemistry was evaluated weekly and doxycycline and rifampicin were also added to the treatment. The patient did not describe any new symptoms and TIA during the treatment period of one year.

**Case 4:** A 28-year-old man was admitted with dysarthria, left hemiparesis and hypoesthesia. The day before this event he experienced multiple attacks of weakness and numbness in the left arm that recovered in five minutes. The diagnosis of brucellosis was made one year ago and antibiotic treatment was started that he did not use regularly. He has had pain in multiple joints for one year, but no vascular risk factors in history. Blood chemistry, blood counts, coagulation profile, and hematologic tests for hypercoagulability were within normal limits, and immunologic markers were negative. MRI of brain showed a frontoparietotemporal infarct with hemorrhagic transformation. Cerebral angiography showed severe stenosis of the right middle cerebral artery. Angioplasty and stenting of the right middle cerebral artery was performed in follow-up of this patient.

On fifteenth day of his admission, right facial paralysis and hearing loss in the right ear
developed abruptly. His physical examination was normal. In neurological examination, there were right peripheral facial paralysis and sensorineural hearing loss in the right ear in addition to his previous findings. CSF analysis was performed (Table 1&2). Blood and CSF cultures yielded Brucella melitensis. The treatment of TMP-SMZ three times a day, doxycycline 200 mg/day and rifampicin 900 mg/day were started. Six months after the initiation of the therapy, he had no additional neurological deficits and was free of TIA and recurrent stroke. CSF analysis revealed no abnormality except for Ig G index in the level of 2.25 and brucella agglutination test in a titer of 1/80.

**Discussion**

Brucellosis, although almost eradicated in many parts of the world, still remains widespread and endemic in the developing countries (1,2,16-18). Neurological involvement during the course of brucellosis occurs in about 2-10% of the cases (1-4). Clinical diagnosis of NB can be very difficult because of various presentations. Several clinical forms of brucellosis affecting the CNS have been reported. These include meningitis, meningoencephalitis, myelitis, myelopathy and demyelination or vascular diseases of CNS (1-9).

The endemic occurrence of brucellosis in this area, positive serology or CSF cultures for brucella, exclusion of other infectious agents and causes of ischemic cerebral symptoms, and good response to treatment with oral antibiotics supported the diagnosis of NB in our patients. Our patients presented with episodes of neurological deficits that were compatible with dysfunction of a certain vascular region and improved in a few hours. Therefore, we defined these episodes as “transient ischemic attacks”. A similar clinical presentation was also reported by other authors and defined as “transient brief attacks” or “intermittent cerebral vascular insufficiency” (1,2,7,19-23). There is some evidence that some of these attacks can be attributed to subarachnoid hemorrhage secondary to ruptured mycotic aneurysm. Transient brief attacks followed by a ruptured basilar artery aneurysm in one patient and accompanied by xanthochromia in another were reported (21,22). A patient describing several attacks of numbness starting in the right foot extending to the right half of the body died of subarachnoid hemorrhage due to ruptured mycotic aneurysm of the basilar artery (7). No evidence of subarachnoid hemorrhage or vascular malformation was found in our patients. Case 4 had TIA resulting in ischemic stroke due to right middle cerebral artery infarct. Then he developed dysfunction of the cranial nerves 7 and 8.

The pathogenesis of TIA and ischemic stroke in brucellosis still remains uncertain. It has been proposed before, that TIA in brucellosis may be related either to infectious vasculitis or cerebral vasospasm or cardioembolism (1,2,19). Various degrees of vascular inflammation ranging from chronic to acute with the possibility of necrosis and aneurysmal formation have been described in CNS brucellosis (7). Carotid angiogram disclosed diffuse vascular spasm in the territory of the middle cerebral artery in a patient with several attacks of numbness starting in the fingers of the right hand extending to the right arm, shoulder and the right half of the face (23). As in ours, most of the patients with ischemic cerebral symptoms in the literature have normal cerebral angiograms (2). Al-Deeb has reported a man who presented with dysarthria and left hemiplegia of acute onset. CT showed a frontotemporal infarct, but cerebral DSA was normal (1). The authors proposed that normal appearance of cerebral vessels in DSA was consistent with vasculitis of deep penetrating arteries (1). We think that cardioembolism does not account for TIA in this series, since cardiac examination and both transthoracic and transoesophageal echocardiographies were normal in all patients.

As a manifestation of basal meningeal infection involvement of one or more cranial nerve has been noted in over one-half of cases (2). The vestibulo-cochlear nerve has been described as the most frequently involved cranial
nerve in NB. Its involvement is usually combined with other neurological dysfunctions (2,16,18,24). Although hearing loss is usually irreversible, further deterioration can be averted by appropriate treatment. Three cases in this series suffered hearing loss with a stable course but no relief after antibiotic treatment, while one patient (Case 4) had facial nerve involvement in addition.

NB may develop at the onset of the illness, during convalescence or months to years after recovery from the acute infection (5,18). Brucellosis was diagnosed in three of our patients previously, and they were treated with antibiotics for a certain period, however none of the patients had systemic manifestations of the disease, such as fever, hepatomegaly, splenomegaly, and lymphadenopathy in physical examination. TIA and ischemic stroke were the predominant manifestations of brucellosis in all patients. Only one of the patients reviewed by us had a focal extraneurologic involvement (sacroiliitis).

The final diagnosis of NB was made on the basis of the serological tests or culture for brucella in CSF. Other criteria supporting our diagnosis were: 1) systemic complaints of brucellosis, such as headache, malaise, weight loss, anorexia, lumbar pain and nausea-vomiting, 2) progressive bilateral sensorineural hearing loss without other known cause, 3) TIA not associated with other well-known risk factors of ischemic stroke, 4) lymphocytic pleocytosis in CSF with increased level of protein, and decreased level of glucose.

Low glucose values, lymphocytic pleocytosis and high protein content and Ig G values are usually found in CSF analysis of NB patients (2). All of our patients had low glucose levels and lymphocytic pleocytosis as an evidence of chronic meningeal inflammation. Three patients had increased protein and Ig G levels in CSF in addition to other abnormal findings. Tuberculosis may cause similar abnormalities in CSF but was excluded with PCR in these cases. In chronic NB increased Ig G index and/or oligoclonal banding pattern in CSF electrophoresis can be detected as in many other chronic inflammatory processes of the CNS (2,16,18). Normal levels of Ig M in serum and CSF were also indicating that infection has reached a chronic stage.

The serological study of both serum and CSF is essential for the diagnosis of NB. The most frequently used method for screening brucellosis is still the standard agglutination test. In active brucellosis high titres of Ig M antibodies can be detected by standard agglutination and Rose-Bengal tests which is followed by an increase of Ig G and Ig A in chronic stage of the disease (2,25). The anti-Brucella Coombs' test is of great value in the diagnosis of chronic NB. We observed that brucella agglutination and Coombs’ tests were the two most common positive tests in CSF in our patients (three patients). As different from the study of Sanchez-Sousa, a positive reaction with Rose-Bengal test (one case) was less frequent than that obtained by the standard agglutination test (25). Case 1 had negative tests for brucella antibodies in CSF but the diagnosis was confirmed by isolation of Brucella species from CSF cultures. It is very unusual that a patient with meningeal inflammation and positive cultures for brucella in CSF had negative serological tests for Brucella antibodies (16). This case shows that CSF cultures for brucella are mandatory to exclude NB in cases with high suspicion of the disease. On the other side, positive CSF cultures are usually difficult to obtain (<20%), sometimes even in the presence of an apparent meningoencephalitis (7,8,16).

TPM-SMZ, rifampicin and doxycycline are the most commonly used antibiotics to treat brucellosis with a good intracellular and CNS penetration. Prolonged treatment (6 months) with a combination of these three antibiotics was used in our patients successfully. Hepatic and renal dysfunction developed only in one patient in the second week of the therapy. However, he tolerated well as the drugs were restarted. TIA discontinued in all patients in the very beginning of the therapy, although some of the abnormal findings in CSF remained unchanged. There is no agreement regarding the ideal duration of
treatment of NB, but it seems reasonable to continue therapy until the patient recovers or remains clinically stable, the CSF glucose return to normal, the CSF cell counts falls and CSF protein and antibodies begin to decrease.

Recognition of TIA and ischemic stroke due to brucellosis and its differentiation from other vascular diseases are not easy, particularly in the elderly patients with stroke risk factors such as hypertension, diabetes, atrial fibrillation etc. We suggest that NB should be always sought in young patients with TIA or ischemic stroke, especially if they do not have any additional risk factors for stroke and live in an endemic area for brucellosis, even if they do not have other
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