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Neurobrucellosis

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Abstract

Brucellosis is a multi-system infectious disease that presents with various clinical manifestations and complications. Neurobrucellosis is an uncommon but serious presentation of brucellosis that can be seen in all stages of the disease. Neurobrucellosis is a focal complication of brucellosis affecting both central and peripheral nervous system presenting varieties of signs and symptoms. The most reported manifestations are meningitis and meningoencephalitis. It is a rare presentation of brucellosis. The estimated mean incidence of neurobrucellosis is 1.7%–10%. The incidence is equal in males and females. Initial clinical manifestations consisted of meningoencephalitis, acute and subacute meningitis, intracranial hypertension, polyradiculoneuritis, cerebral and subarachnoid hemorrhage, transverse myelitis, lumbar epidural abscess with root involvement, and cranial nerve involvement. Other rare manifestation includes pseudotumor cerebri, intracranial granuloma, sagittal sinus thrombosis, spinal arachnoiditis, and intracranial vasculitis. High index of suspicion, especially in endemic areas is essential to prevent morbidity from this disease. Clinical suspicion and accurate evaluation of a patient's history is the most important clue in diagnosis and treatment. Neurobrucellosis can be diagnosed by isolation of microorganism from the CSF or detection of antibodies in the CSF. The CSF pattern in neurobrucellosis can be helpful for diagnosis; lymphocytic pleocytosis, increased protein, and decreased glucose levels in the CSF are in favor of neurobrucellosis. Imaging modalities, including CT scan or magnetic resonance imaging, may reveal information for diagnosis. Many laboratory procedures are usually employed in the diagnosis of neurobrucellosis. Even though the culture method is the gold standard, growth rate is low and time consuming. Coombs' test should be performed in both the CSF and serum. Different regimens are usually used based on ceftriaxone, doxycycline, cotrimoxazole, streptomycin, and rifampicin. Treatment with intravenous ceftriaxone and oral rifampicin, doxycycline, and trimethoprim–sulfamethoxazole resulted in a good clinical response. Patients with severe and persistent headache and other neurologic symptoms and signs should be considered for neurobrucellosis in endemic regions. Early diagnosis and treatment of neurobrucellosis will be helpful in decreasing the sequelae of this complication.

Keywords: Neurobrucellosis, clinical manifestation, diagnosis, treatment

1. Introduction

Brucellosis is a common zoonotic infection worldwide and is caused by *Brucella* species. Central nervous system (CNS) involvement is a serious complication of brucellosis with different clinical presentation [1]. Neurobrucellosis is a focal complication of brucellosis affecting both central and peripheral nervous system (PNS) presenting with a variety of signs and symptoms [2]. Neurologic involvement due to brucellosis was reported in 1.7%–10% of the patients with brucellosis [3, 4, 5]. Neurological complications of brucellosis are divided into two groups. The first are those that have a direct effect of microorganism on the CNS and PNS, and the second are those that have indirect effect of brucellosis on the CNS or PNS, e.g., toxic-febrile neurobrucellosis [6].

2. Clinical manifestations

Neurobrucellosis can affect any part of the nervous system and can mimic any neurological disease [7]. The most reported manifestations of neurobrucellosis are meningitis and meningoencephalitis [2]. Neurobrucellosis may also present as myelitis, myelopathy, stroke, paraplegia, radiculoneuritis, intracerebral abscess, epidural abscess, intradural abscess, demyelination, Guillain-Barré syndrome, polyneuritis, and cranial nerve involvement or any combination of these manifestations [3, 8, 9, 10]. Neurobrucellosis affects the second, third, sixth, seventh, and eighth cranial nerves. Involvement of the oculomotor nerves is a very rare complication in neurobrucellosis [11]. Optic neuritis due to neurobrucellosis has been reported [12]. Neurobrucellosis can cause hearing loss. It may affect the auditory pathway. Sensorineural hearing loss can be seen due to brucellosis. Cochlear implantation may be successful for treatment of patients with sensorineural hearing loss [13]. Neurobrucellosis may present rarely with communicating hydrocephalus with symptoms of headaches, nausea, vomiting, gait disturbance and signs of dysmmetry, ataxia, and sensorineural hearing loss [14]. Spastic paraparesis and the sensorineural involvement are rare manifestations [8]. Solitary intracranial mass lesions mimicking cerebral tumor are extremely rare presentations of neurobrucellosis [15]. It may also present as leukoencephalopathy [16]. Cerebral venous sinus thrombosis due to brucellosis is a rare form of stroke caused by thrombosis in venous sinuses of the brain [17]. Sagittal sinus thrombosis is one of the manifestations [18]. Neurobrucellosis is associated rarely with demyelination. It may involve the corpus callosum [19]. Spinal epidural abscess due to the *Brucella* species is usually associated with spondylodiscitis. Urgent surgical decompression should be performed in cases with moderate to severe neurological deficits particularly if progressive [20]. Quadriplegia and multiple brain abscesses have been reported as manifestations of neurobrucellosis [21]. There are reports of intramedullary brucellar granuloma as rare cases of neurobrucellosis. Nas et al. reported a patient presented with loss of strength of four extremities. An intramedullary mass lesion was detected in the cervical level and brucellar granuloma of the cervical spine was diagnosed finally [22]. In Asadipouya's study on neurobrucellosis, headache, fever, neck rigidity, fatigue, altered mental status, speech disturbances, nausea, and vomiting were the most common symptoms. Hearing loss, paraplegia, cerebellar ataxia, diplopia, photophobia, blurred vision, abnormal behavior, hypoesthesia, low back

pain, and right side weakness are categorized as less common clinical features [6]. An analytical study on several publications on neurobrucellosis demonstrated that the most frequent symptoms of neurobrucellosis are fever, headache, weight loss, sweating, and back pain; and the most frequent signs of neurobrucellosis are meningeal irritation, confusion, hypoesthesia, hepatomegaly, and splenomegaly. Crainial nerve involvement, polyneuropathy, polyradiculopathy, paraplegia, and abscess formation may occur during neurobrucellosis. Symptom duration may vary between one week and six months [23, 24]. Patients with neurobrucellosis may present with neuropsychiatric signs and symptoms including aphasia, diplopia, hemiparesis, facial paralysis, tremor, ataxia, depression, personality disorder, hallucinations, agitation, behavioral disorders, muscle weakness, and disorientation [25, 26]. Shehata's study demonstrated that CNS involvement (vascular stroke, meningoencephalitis, and dementia) was seen in 33% of patients and PNS involvement (polyneuropathy, radiculopathy, and polyradiculoneuropathy) was seen in 22% of patients. Depression was recorded in 29% of patients. Patients with neurobrucellosis reported highly significant impairment in some cognitive function measures (mental control, logical memory, visual reproduction) and higher scores on depressive symptoms compared with controls [27]. Brucellosis may infect ventriculo-peritoneal shunt [28]. The mean duration of symptoms before admission is 8 weeks (range: 1 week–4 months) [6]. In neurobrucellosis, CNS invasion by bacteria results in an inflammatory disorder. During neurobrucellosis, microglia and astrocytes may be involved. The results of these involvements are production of pro-inflammatory cytokines that are harmful for CNS. Matrix metalloproteinases (MMP) has been found in the inflammatory process of CNS. Pro-inflammatory cytokines cause increased production of MMP. During neurobrucellosis, astrogliosis occurs [29]. Inflammatory response elicited by *Brucella* in astrocytes would lead to the production of MMP-9 and that mitogen-activated protein kinases may play a role in this phenomenon. Mitogen-activated protein kinases inhibition may thus be considered as a strategy to control inflammation and CNS damage in neurobrucellosis [30]. *Brucella* lipoproteins could be key virulence factors in neurobrucellosis and that astrogliosis might contribute to neurobrucellosis pathogenesis [31].

3. Complications

Recovery of neurobrucellosis may accompany with sequela. Paraparesis, dementia, sphincter dysfunction, peripheral facial paralysis, and sensorineural hearing loss may occur [10, 25].

Communicating hydrocephalus has been reported as a complication of neurobrucellosis that may need external ventricular drainage [32]. Mild sequelae, including aphasia, hearing loss, and hemiparesis, may remain after successful treatment [33]. The mortality of neurobrucellosis can be up to 0.5% with suitable antibiotics [24].

4. Diagnosis

Clinical suspicion and accurate evaluation of a patient's history is the most important clue in the diagnosis and treatment of brucellosis [17]. Early detection and treatment is an important

predictor of favorable outcome of neurobrucellosis [7]. Diagnosis requires a high index of suspicion in patients from endemic areas. Diagnosis is often based on neurological symptoms, serology, and suggestive brain imaging [34]. In patients with laboratory-confirmed brucellosis, the neurobrucellosis may be diagnosed with one of these criteria: first, signs and symptoms of neurobrucellosis include fever, headache, and cranial nerve palsies; second, CSF abnormality compatible with brucellosis including CSF lymphocytic pleocytosis, low glucose, and high protein levels of CSF detection of anti-Brucella antibodies in the CSF or isolation of Brucella from the CSF; third, imaging abnormality compatible with brucellosis especially in CT scan and MRI [25].

In a study on patients with neurobrucellosis, criteria for diagnosis was defined as: 1) neurobrucellosis clinical manifestation; 2) CSF abnormality (lymphocytosis, decreased glucose, increased protein); 3) positive anti-brucella antibody in the CSF or serum; 4) clinical response to empirical therapy; and 5) no other diagnosis compatible with signs and symptoms [6]. The sensitivity of tube agglutination in the CSF is 0.94, specificity 0.96, positive predictive value 0.94, and negative predictive value 0.96 [25].

In Erdem's study on 177 patients with neurobrucellosis mean values of the CSF, biochemical test results were as follows: CSF leucocyte count=215, CSF protein=330 mg/dL, CSF/blood-glucose ratio=0.35. The sensitivity of serum standard tube agglutination was 94%; CSF standard tube agglutination was 78%. Blood culture was positive for brucellosis in 37% by automated method and CSF culture was positive in 25% and 9% by automated and conventional CSF culture, respectively [35]. Another study showed the CSF WBC count to be between 6 cells/dl and 3600 cells/dl with mean count of 403 cells/dl. Most of the patients had CSF lymphocyte predominance and some had CSF polymorphonuclear predominance. Elevated CSF protein (>45 mg/dl) was detected in about 90% of the patients. CSF low glucose level (<40 mg/dl or CSF/Serum glucose ratio of <0.4) was seen in about half of the patients [6]. Yetkin's study demonstrated that the mean count of CSF WBC was 244 with high CSF protein level in all patients and low CSF glucose level in half of the patients [23]. Brucella bacteria may be isolated from CSF in only 15% of the patients. Brucella tube agglutination with Coombs test in the CSF is sensitive and specific [25]. Serum agglutination test is often used for screening and as a complement fixation test for confirmatory tests. Enzyme-linked immunosorbent assay (ELISA) for brucella is more sensitive and specific than other serological tests and it may replace other serological tests. ELISA may detect antibodies against brucella in the serum and CSF. A patient with neurobrucellosis may have negative serological markers of brucellosis in the CSF and serum. Serum anti-brucella immunoglobulin G (IgG) and immunoglobulin M (IgM) antibody may be checked using the ELISA method for patients who had negative Coombs' Wright agglutination tests results [6]. Adenosine deaminase (ADA) activity in the CSF of patients with brucella meningitis can be used for diagnosis. CSF ADA activity with cut-off value of 12.5 IU/L has a sensitivity of 92% and specificity of 88% for diagnosis of brucella meningitis [36]. When cerebrospinal fluid culture is negative, PCR may be an optimal alternative tool for an immediate and accurate diagnosis [37]. Imaging findings of neurobrucellosis is divided into four categories: (1) normal, (2) inflammation (recognized by granulomas, abnormal enhancement of the meninges, perivascular space, or lumbar nerve roots), (3) white matter changes, and (4) vascular changes [38]. Infarct in the anterior limb of the left internal

capsule and putamenal infarctions has been reported due to brucellosis. The diagnosis of neurobrucellosis can be considered despite negative CSF culture and serology based on clinical response and resolution of CSF abnormality with anti-brucella treatment [6]. Tekin-Koruk reported a seronegative neurobrucellosis case with depression and diplopia. Results of agglutination tests for *Brucella* both in the serum and CSF were negative. Diagnosis was made only by positive culture of *Brucella mellitensis* with inoculation of the patient's cerebrospinal fluid in a BACTEC 9050 System [39].

5. Treatment

Neurobrucellosis is a treatable disease with a favorable outcome. Doxycycline, rifampicin, ceftriaxone, trimethoprim sulfamethoxazole, ciprofloxacin, and streptomycin have been found effective in neurobrucellosis [6]. An important challenge in treatment of brucellar meningitis or meningoencephalitis is that patients should be treated with oral antibiotics or whether an intravenous extended-spectrum cephalosporin, such as ceftriaxone, which does not accumulate in phagocytes, should be added to the regimen. Several different protocols have been used for treatment. Ceftriaxone, rifampin, and doxycycline or trimethoprim-sulfamethoxazole, rifampin, and doxycycline have been used for treatment. Ceftriaxone-based regimens are more successful and require shorter therapy than the oral treatment protocol [40]. Treatment protocol in Karsen's study consisted of ceftriaxone, rifampicin, and doxycycline for a period of four weeks, followed by rifampicin and doxycycline for an additional four weeks [26]. Duration of treatment will depend on the patient's condition. If rapid improvement occurs, we may shorten the duration of antibiotic therapy to 12 weeks and continue their treatment by clinical assessment. In the study by Bodur, all patients received antibiotic therapy with ceftriaxone, rifampicin, and doxycycline initially and after one month they were continued with rifampicin and doxycycline up to four months. Oral Doxycycline and rifampin with intravenously ceftriaxone are the most common antibiotics in the treatment of neurobrucellosis [6]. Gul's study demonstrated that parenteral ceftriaxone should be used as an initial alternative in the management of neurobrucellosis [41]. Duration of treatment varies in different studies ranging from several weeks to several months. In Ceran's study, duration of treatment varied between 3 and 12 months according to the CSF response [33]. According to Gul's study, it is recommended that the duration of therapy should be a minimum of six months with suitable antibiotics, although the therapy should be individualized [41]. In contrast, in Asasipouya's study in Iran, duration of treatment was as short as eight weeks in about half of the patients. Short course treatment in neurobrucellosis is possible in patients with meningoencephalitis who do not have any focal neurologic deficit or have minimal deficit. Other patients need treatment for a long duration according to neurologic manifestations [6].

6. Conclusion

Patients with severe and persistent headache and other neurologic symptoms and signs should be considered for neurobrucellosis in endemic regions [25]. It should be included in differential

diagnosis for any patient presenting with central or peripheral neurological manifestations especially in endemic areas [7]. With early diagnosis and treatment, neurobrucellosis has a good outcome with no or minimal neurologic complications. The duration of disease and the time between starting symptoms and starting antibiotic influences the prognosis [6].

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