

Short-course treatment in neurobrucellosis: A study in Iran

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Abstract

Neurobrucellosis is a rare neurological complication of brucellosis. This report describes 19 patients of neurobrucellosis and they accounted for 8% of all cases of brucellosis admitted to Shiraz University Hospitals over a period of eight years. Headache, fever, fatigue, drowsiness and neck stiffness were the common clinical features. Cerebrospinal fluid (CSF) showed pleocytosis in 100%, elevated protein levels in 89% and low glucose level in 47% of the patients. All the patients improved with specific antibiotic treatment. Of the 19 patients, 10 (52.5%) patients received treatment for 8 to 28 weeks. Duration of antibiotic treatment was: 8-14 weeks in 8 (42%) patients; 24-28 weeks in 2 (10.5%) patients; 6 months in 7 (37%) patients; 12 months in 1 (5.3%) patient; and 18 months in 1 (5.3%) patient. Clinicians in endemic areas should consider the likelihood of neurobrucellosis in patients with unexplained neurological and psychiatric symptoms.

Key words: Neurobrucellosis, short course, treatment

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Introduction

Central nervous system (CNS) involvement is a serious complication of brucellosis.^[1] Neurobrucellosis occurs in 5-10% of cases of brucellosis.^[2] Neurological complications can be categorized into two major groups: 1) those related to the acute-febrile phase of the illness, toxic-febrile neurobrucellosis and 2) those related to primary affection of central and peripheral nervous system by the brucella infection.^[2] CNS involvement is commonly acute and results mainly in meningoencephalitis, while peripheral nervous system (PNS) involvement may be either acute or chronic.^[3] In this article, we report the clinical characteristics and treatment strategies of 19 patients with neurobrucellosis.

Material and Methods

This is a retrospective study of patients with neurobrucellosis admitted to two tertiary care hospitals in Shiraz, Iran over a period of eight years. Diagnostic criteria for neurobrucellosis were: 1) clinical features compatible with a known neurobrucellosis syndrome; 2) typical cerebrospinal fluid (CSF) (elevated protein concentration or pleocytosis) findings; 3) positive blood or CSF serology for brucellosis (e.g., agglutination test titers of >1:160 in blood or any positive titer in CSF); 4) clinical improvement with a course of antibiotic therapy; and 5) clinical syndrome otherwise not explainable by an alternative diagnosis. Case records were reviewed and the data collected included clinical features, laboratory data, neuroimaging findings, treatment details, and outcome. Serum anti-brucella immunoglobulin G (IgG) and immunoglobulin M (IgM) antibody were checked for patients who had negative Coomb's Wright agglutination tests results by enzyme-linked immunosorbant assay (ELISA) method. Antibiotic treatment included: doxycycline, rifampin, trimethoprim-sulfamethoxazole, streptomycin, gentamicin and ceftriaxone. Treatment was discontinued after clinical assessment by the

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physicians when they were certain that the infection was controlled. All patients were followed for two years to find any signs and symptoms of relapse.

Results

Of the 235 patients with brucellosis admitted during the study period, 19 (8%) patients had neurobrucellosis. Mean age was 38.1 years (range 18 - 70 years) and there were 14 (74%) were males. The mean duration of symptoms before admission was 8 weeks (range 1 week - 4 months). The most common clinical features were: headache (79%), fever (84%), neck rigidity (42%), fatigue (37%), altered mental status (31%), speech disturbances (21%), nausea and vomiting (15%). Other less common clinical features were hearing loss, paraplegia, cerebellar ataxia, diplopia, photophobia, blurred vision, abnormal behavior, hypoesthesia, low back pain and right-side weakness. Ten (58%) patients had focal neurological deficits.

CSF analysis showed elevated protein (> 45 mg/dl) in 17 (89%) patients. low glucose (< 40 mg/dl and/or CSF/serum glucose ratio of < 0.4) in nine (47%) patients. CSF WBC count was between 6 cells/dl and 3600 cells/dl with mean count 403 cells/dl. Fifteen (79%) patients had lymphocyte predominance and four (21%) patients had polymorphonuclear (PMN) predominance. CSF cultures and Gram-stains were negative in all patients. Of the six sera tested for anti-brucella antibody, 3 (50%) were positive. Anti-brucella antibodies in the CSF by either ELISA or Coomb's Wright agglutination tests were tested in 9 patients that was positive in 6 (67%) patients.

Three patients had electrodiagnostic evidence of peripheral neuropathy. Brain computed tomography (CT) scan was done in 12 patients; only one scan showed infarct in the anterior limb of left internal capsule. This patient had right hemiparesis. Brain magnetic resonance imaging (MRI) was performed in eight patients with normal brain CT scan. Scans in two patients showed abnormalities; (1) a-23-year old male with one history of hearing loss and three month history of severe headache showed mild hydrocephalus with right temporal atrophy; and (2) a-27-year old male with one week history of fever, headache, inappropriate speech, abnormal behavior, and seizures showed putamenal infarctions.

Eight (42%) patients who presented with fever, headache and/or drowsiness and no focal deficits, received 8-14 weeks' antibiotic therapy (doxycycline, rifampin and trimethoprim-sulfamethoxazole or streptomycin or ceftriaxone). Two patients with hearing loss had received 24 and 28 weeks of antibiotics respectively

(doxycycline, rifampin, trimethoprim-sulfamethoxazole and ceftriaxone for the first month). Both the patients improved significantly in their hearing as shown in the followup audiometric studies. One patient with lower extremity weakness and peripheral neuropathy received 1.5 year antibiotic therapy (doxycycline, rifampin and trimethoprim-sulfamethoxazole). One patient with headache and photophobia with normal brain CT scan and brain MRI received one month doxycycline, rifampin and streptomycin. Treatment was continued by doxycycline and rifampin for 11 months. Seven patients (37%) had received six months' antibiotic therapy with doxycycline, rifampin and trimethoprim-sulfamethoxazole or ciprofloxacin or gentamicin (ceftriaxone for the first month). All the patients improved without any sequela and none had relapse during the two years' follow-up. Follow-up was done by visiting the patients and also by telephone. There were no side-effects related to long-term aminoglycoside therapy. Mild transient elevation of liver enzyme occurred in some patients with rifampin. One patient died in the second year because of a cardiac event at the age of 70.

Discussion

Brucellosis is a multisystem disease with a broad spectrum of clinical manifestations.^[4] It is a common zoonosis in many parts of the world and is not uncommon in Iran. Neurobrucellosis accounted for 8% of all cases of brucellosis and is comparable to the reported frequency 5-10% in the earlier studies.^[5,6] Headache, fever, sweating, weight loss, and back pain are the predominant symptoms in neurobrucellosis.^[1,7] Meningitis and meningoencephalitis are the most common forms of neurobrucellosis.^[8] Other neurological complications including myelitis, radiculoneuritis, brain abscess, epidural abscess, meningovascular syndromes, subarachnoid hemorrhage and psychiatric manifestations.^[9] In our study meningitis and meningoencephalitis were the most common presentations. In this study the main reasons for delay in the diagnosis were less severe symptoms and lack of awareness of neurobrucellosis among the practicing physicians in this part of the world.

Serum agglutination test is often used for screening and complement fixation or Coombs' test are confirmatory tests. 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.^[10-12] A patient with neurobrucellosis may have negative serological markers of brucellosis in the CSF and serum.^[13] Lymphocytic pleocytosis and elevated proteins in CSF were the common abnormalities in our series. 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.^[13]

Neurobrucellosis is a treatable disease with a favorable outcome. Doxycycline, rifampicin, ceftriaxone, trimethoprim sulfamethoxazole, ciprofloxacin and streptomycin have been found effective in neurobrucellosis.^[14-16] Duration of treatment can depend on 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 *et al.*,^[14] 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. Doxycycline (by mouth) plus rifampin (by mouth) with ceftriaxone (intravenously) were the most common antibiotics in the study by Demiraslan *et al.*^[17] Most of our patients received antibiotic treatment for 24 weeks and an acceptable response was seen within 12 weeks in seven (36%) patients. Short course of antibiotic therapy may be an option in patients with meningoencephalitis with no focal deficits or with minimal deficits. Patients with longer duration of the disease or with significant neurological deficits may require antibiotic treatment for a longer duration. Neurobrucellosis has an excellent prognosis when treated early and appropriately. The neurologic sequelae may be minimal. The important prognostic factors are duration of the disease, virulence of the microorganism and timing of antibiotic therapy. Early diagnosis and early institution of treatment is associated with fewer sequelae.

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1. Gul HC, Erdem H, Bek S. Overview of neurobrucellosis: A pooled



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