

## Clinical and laboratory findings in neurobrucellosis: A study of 43 cases

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### ABSTRACT

**Background:** Brucellosis is a common zoonotic infection that is endemic in many parts of the world. Neurological involvement is a rare entity, occurs in 2-5% of cases. Neurobrucellosis comprises a variety of complications, including meningitis, meningoencephalitis, myelitis and myelopaties, peripheral and cranial neuropathies, and psychiatric manifestations. The aim of the present study was to evaluate neurological manifestations and cerebrospinal fluid (CSF) findings in a group of Iranian patients with neurobrucellosis.

**Materials and methods:** During a 10-year period (1996-2005), medical records of 43 hospitalized patients with definite diagnosis of neurobrucellosis were studied. Inclusion criteria were a minimum titer of 1/160 for Wright and abnormal CSF findings. Age, gender, neurological manifestations, CSF analysis and its changes were investigated.

**Results:** Neurological manifestations include meningitis (64.9%), meningoencephalitis (11.6%), cranial nerve palsy (11.6%), brain abscess (2.4%), myelitis (2.4%) and psychiatric disorders (6.9%). Pleocytosis (100%), high protein (40%) and low glucose levels (40%) were noted in CSF analysis.

**Conclusion:** Clinical manifestations and CSF abnormality of neurobrucellosis is similar to tuberculosis and neurobrucellosis must be kept in mind in approach of patients with acute or chronic lymphocytic meningitis with increased protein and low glucose level in CSF and risk factors of brucellosis.

**Keywords:** *Neurobrucellosis, Brucella meningitis, Brucellosis.*

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### INTRODUCTION

Brucellosis is a common zoonotic infection in many parts of the world, including Middle Eastern countries. Iran is an endemic country for brucellosis (1). Human brucellosis is a multisystem disease that may present with a broad spectrum of clinical manifestations. Musculoskeletal, genital, cardiac, respiratory and nervous systems are involved (2). Neurobrucellosis may develop at any

stage of the disease and may have widely variable manifestations. The clinical neurological syndromes which may be caused by *Brucella* include, acute toxic manifestations, meningitis, diffused or localized encephalitis, myelitis, radiculitis, neuritis, multiple cerebral or cerebellar abscesses, ruptured mycotic aneurysm and subarachnoid hemorrhage, Guillain-Barre syndrome, cranial nerve palsies, hemiplegia, sciatica, myositis, and rhabdomyolysis. Furthermore, papillitis, papilledema, retrobulbar neuritis, optic atrophy and ophthalmoplegia due to lesion in cranial nerves III, IV, and VI may occur

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in brucella meningoencephalitis (3). The most common neurological manifestation is a subacute or chronic meningoencephalitis, however, many other CNS manifestations of neurobrucellosis have been reported: arachnoiditis, cerebellar syndromes, ruptured basilar aneurism, hemiparkinsonism, chorea, and anterior poliomyelitis. Sometimes it may mimic brain tumor signs. Acute toxic manifestations are seen during the acute phase of infection, and include headache, neckache, insomnia, depression and muscle weakness. Motor manifestations occur frequently and generally present in the form of paresis of variable intensity, with frequent gait disturbances. Sensory symptoms usually consist of paresthesia and occasional gait apraxia. Involvement of the cranial nerves, generally the 6<sup>th</sup>, 7<sup>th</sup>, and 8<sup>th</sup> is reported as a very characteristic of the brucella meningitis (4).

This study was designed to determine the neurological manifestations and CSF finding in a group of Iranian patients with neurobrucellosis.

### PATIENTS and METHODS

This retrospective study was conducted in the Infectious Diseases and Tropical Medicine Research Center of Tabriz University of Medical Sciences for a period of 10 years (from 1996 to 2005). A total of 43 patients (28 males and 15 females) had definite diagnosis of neurobrucellosis.

Lumbar puncture was achieved in patients with the diagnosis of brucellosis if one of the following complaints occurred: severe headache, insomnia (sleep disorder), urinary incontinence, neck stiffness, confusion, neurological manifestations, depression and change in personality.

Neurobrucellosis was diagnosed by the following criteria: 1- symptoms and signs compatible with neurobrucellosis (history of potential exposure, a presentation consistent with the Brucellosis suffered neuropsychiatric complications and supporting laboratory findings, 2- abnormality of CSF, 3- demonstration of

antibodies against Brucella in the CSF. Patients who lacked CSF abnormality and serum agglutinin titer of <1/160 were excluded.

Gram and Ziehl-Neelsen stains, VDRL and India ink preparation for cryptococcus neoformans were routinely carried out on the CSF. In addition, blood, bone marrow and CSF were cultured for conventional bacteria (TB) and fungi. If fever of unknown origin (FUO) was suspected, bone marrow culture was performed. Chest radiograph and PPD skin test were done in order to rule out tuberculosis.

Brain and spine CT scanning was undertaken in all cases to find out any pathologic variations in the CNS.

### RESULTS

The study population included 28 males and 15 females with a mean age of 34.4±20.7 years (a range, 12-81 years). All patients showed a history of exposure to a possible source of infection.

Neurological manifestations include: meningitis (64.9%), meningoencephalitis (11.6%), brain abscess (2.4%), meningitis with cranial nerve palsy (11.6%), myelitis (2.4%) and psychiatric disorders (6.9%). Meanwhile, the most common clinical findings were: fever, headache, nausea and vomiting, dizziness, back pain, rigor, neck pain, insomnia, arthralgia, sciatalgia, neck stiffness, Kernig's sign, Brodzinski's sign, convulsion, hepatomegaly, splenomegaly, cranial nerve involvement (6<sup>th</sup>, 7<sup>th</sup> and 8<sup>th</sup>), and urinary incontinence (table 1).

Totally, 70% of patients had chronic and 30% had acute presentation. Three patients had only psychiatric disorders.

One patient was admitted because of paresthesia, leg weakness, urinary retention, sensory abnormality, paraplegia, fever, sweating, and hepatosplenomegaly for whom brucella myelitis was established with MRI, serology and blood culture.

**Table 1.** *Distribution of signs and symptoms of neurobrucellosis*

Signs		Symptoms	
<b>Fever</b>	33 (76.9) *	<b>Sweating</b>	34 (78.9)
<b>Neck stiffness</b>	9 (20.9)	<b>Headache</b>	30 (69.6)
<b>splenomegaly</b>	16 (37.1)	<b>Nausea-vomiting</b>	17 (39.4)
<b>Hepatomegaly</b>	14 (32.5)	<b>Neck pain</b>	12 (27.5)
<b>Kernig</b>	12 (27.5)	<b>Back pain</b>	12 (27.5)
<b>Brudzinski</b>	11 (25.5)	<b>Arthralgia</b>	11 (25.5)
<b>Rigor</b>	7 (16.2)	<b>Dizziness</b>	10 (23.2)
<b>Convulsion</b>	4 (9.3)	<b>Sciatalgia</b>	6 (13.9)
<b>Cranial nerve involvement</b>	4 (9.3)	<b>Insomnia</b>	4 (9.3)
<b>Incontinence</b>	1 (2.3)		
<b>Leg weakness</b>	1 (2.3)		
<b>Paraplegia</b>	1 (2.3)		
<b>Urinary retention</b>	1 (2.3)		

\* Numbers in parenthesis are percentage

Full blood count was performed for all patients. The mean obtained values were: hemoglobin 11.2gr/dl (9.8–16.1 gr/dl), WBC  $5.4 \times 10^3$ /cc (3.6–11.2), lymphocyte 42% (25–52%), and erythrocyte sedimentation rate (ESR) 26 (10-50).

Lumbar puncture confirmed lymphocytic pleocytosis in all patients. Reduced CSF glucose in 40% patients and increased protein content (60–270mg/cc) in 40% patients was also remarkable. Despite CSF abnormality of patients, standard agglutination test of CSF was performed for all patients and revealed to be positive in 60% (26 cases). Wright test titer of CSF ranged 1/80–1/640. CSF serology was negative in 40%. Standard agglutination test of blood samples was positive in all patients (a range, 1/160–1/5640). Blood, CSF and bone marrow cultures were positive in 3, 3, and 2 patients, respectively.

Fortunately, all patients, except 2, improved completely with at least a 3-month treatment protocol (with three drugs regimen). One patient referred with relapse after two months, however,

cured with re-treatment, and the other patient died because of brain abscess.

## DISCUSSION

The central nervous system (CNS) is involved in 5-7 percent of cases of brucellosis which often has an ominous prognosis (5). Meningitis, encephalitis, meningoenkephalitis, brain abscesses, meningovascular disease, demyelinating syndromes and psychiatric manifestation have all been reported (5-7).

Fincham classified neurobrucellosis in to four main groups: meningoencephalitis, subarachnoid haemorrhage due to ruptured mycotic aneurysm, myelitis and myelopathy and neuritis. Brucella-induced parkinsonism and non parkinsonian tremor and rigidity has been described. Psychiatric complications due to brucella toxin occur in any group of brucellosis (8).

The pathology of meningoencephalitis is direct effect of the organism or its products on the meninges and brain. Myeloradiculopathy can result from infection arachnoiditis of the spinal cord or infectious vasculitis, leading to medullary infarct (9).

Chronic meningitis might be due to persistent intracellular effects of the organism or perhaps the infection might trigger an immune mechanism leading to demyelination (9-11).

Neurobrucellosis can result in a number of nervous system manifestations. The most common presentation is a typical meningitis or meningoencephalitis that has an acute onset and can occur either as the only site of infection or in the context of systemic disease (12). Patients with acute infection can have cranial nerve palsies that usually resolve completely with antibiotics, whereas those with chronic CNS infection often have permanent neurological deficits. The various chronic manifestations are perhaps best divided into those presenting with peripheral neuropathy or

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radiculopathy and those presenting with more diffuse CNS involvement that include myelitis with cranial nerve involvement and a syndrome of parenchymatous dysfunction (13). Symptoms of the peripheral neuropathy and radiculopathy include back pain, areflexia, and paraparesis with involvement of the proximal nerve radicals. In patients with diffuse CNS involvement, myelitis is evidenced by back pain, spastic paraparesis, and demyelination and can also occur with cerebellar dysfunction. The syndrome of parenchymatous dysfunction can occur at any site in CNS but most commonly affects the cerebellum, spinal cord, and cerebral white matter. Meningovascular complications, in particular mycotic aneurysms, ischemic strokes, and subarachnoid hemorrhage, are relatively common (14).

Chitra et al reported the clinical course and immune system response of patient with disease associated recurrent transverse myelitis following cerebral infection with brucellosis melitensis. The patient suffered four recurrences of this transverse myelitis over the course of 2 years following his initial presentation. Marked elevation of IL-6, IL-8 and macrophage chemoattractant protein (MCP-1) level in CSF of patients with transverse myelitis due to brucellosis was observed. Quantitative enzyme-linked immunosorbent assay (ELISA) analysis of the CSF confirmed a 1700-fold elevation of IL-6 and more modest elevations of IL-8 and MCP-1 (15).

The most typical presentation of CNS involvement in brucellosis is chronic meningoencephalitis with mononuclear pleocytosis, low glucose and increased protein concentration in CSF (16).

Seidel et al reported a 65 years old Iranian immigrant man living in the United State with the diagnosis of neurobrucellosis presenting as leukoencephalopathy (17).

Bingol reported a series of four cases presented with transient ischemic attacks as the predominant manifestation of neurobrucellosis. The

pathogenesis of TIA and ischemic stroke in neurobrucellosis still remains uncertain. It has been proposed before, that TIA in neurobrucellosis may be related either to infectious vasculitis or cerebral vasospasm or cardioembolism. Uncommon clinical presentation of neurobrucellosis such as migraine, parkinsonism, optic neuritis, chronic intracranial hypertension and epilepsy were described. Brucella meningitis may also behave as an exclusively neurological disease, mimicking vascular accidents or neurological diseases that are frequency paroxysmal and recurrent (18).

Al-Tahan reported a 23 years old woman with a one year history of recurrent brucellosis presented with headache, neck pain, vomiting, photophobia, papilledema. She had leukocytosis and a high erythrocyte sedimentation rate (ESR). Brain MRI and magnetic resonance angiography revealed complete sagittal sinus thrombosis (19).

Vajramant et al have reported a 40-year old female presented with progressive weakness of both lower limb and urinary incontinence lasting for 6 months. Neurological examination of the patient revealed flaccid areflexic paraplegia with T<sub>10</sub> below sensory impairment including perianal region. An intramedullary mass was diagnosed on MRI scan extending from T<sub>12</sub> to L<sub>2</sub>. At surgery, a large abscess was encountered at the conus medullaris, from which Brucella melitensis was grown on culture (20). Mass lesions within the brain parenchyma are extremely uncommon but Sohn et al reported two patients with intracerebral granuloma caused by Brucella spp (21).

There may be no history, for example of drinking unboiled milk or animal contact to alert the clinician to the possibility of brucellosis (22). The serologic study of both serum and CSF will usually reveal abnormality in brucella meningitis or encephalitis but the degree of abnormality varies and is not specific. CSF pressure is usually elevated, and CSF may appear clear, turbid or hemorrhagic. Often there is a CSF pleocytosis with lymphocyte predominating CSF. Pleocytosis is

seen in 91% of cases of brucella meningitis. The protein content is usually raised and the sugar content may be reduced or normal. Antibody against *Brucella* may be demonstrated in CSF by ELISA (23). Most patients mount significant serologic response to brucella infection, the most frequently used test is standard tube agglutination test (SAT). The detection of brucellar antibodies in the CSF is always indicative of local infection. CSF titers are, however, much lower than those in serum in cases of systemic brucellosis. Coombs' test may provide the only positive data for CSF when results of agglutinin tests are negative. The screening of antibodies by Coomb's test in CSF is the most reliable serologic test for the diagnosis of brucella meningitis. No single titer of brucellar antibodies is diagnostic, however, most cases of active infection have titers higher than 1:160 in CSF. The febrile agglutination tests are insensitive and should not be relied on for diagnosis. In any suspected case of brucellosis attempts should be made to culture the organisms, although cultures are positive in less than one quarter of cases. Gram stains are usually negative. ESR is increased in <25% of patients and white blood cell count is often normal or low (24). Diaz et al have shown an elevation of CSF oligoclonal IgG in patients with brucella meningitis (25).

CT appearances of brucella meningitis and encephalitis are similar to other bacterial meningitides (26).

Morata et al evaluated diagnostic yield of a PCR assay in focal complications of brucellosis. Their results showed that PCR has high sensitivity and specificity in diagnosis of localized brucellosis such as neurobrucellosis in comparison with seroagglutination test and culture. Low degree of sensitivity of the seroagglutination test for the focal forms of brucellosis is due to the longer duration of the clinical picture in these patients (27).

Colmenero et al compared PCR in CSF with conventional microbiologic techniques in six patients with neurobrucellosis. All six patients

were positive by PCR assay, whereas CSF culture and seroagglutination test were positive in only two and four cases, respectively. Result of their study showed that PCR could be useful for rapid diagnosis of neurobrucellosis (28).

In conclusion, most of our reported manifestations are in conformity with the literature, however, further surveys are recommended for a more meticulous outcome. Clinical manifestations and CSF abnormality of neurobrucellosis is similar to tuberculosis and neurobrucellosis must be in our mind in approach of patients with acute or chronic lymphocytic meningitis with increased protein and low glucose level in CSF and risk factors of brucellosis.

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