CLINICAL, EPIDEMIOLOGICAL, LABORATORY AND IMAGING ASPECTS OF BRUCELLOSIS WITH AND WITHOUT NEUROLOGICAL INVOLVEMEN

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Abstract- Brucellosis is an endemic infectious disease in our country. Neurobrucellosis occurs in 5 to 10% of cases, and can present at any stage of acute or chronic phases of the disease. This study was undertaken to evaluate clinical, epidemiological and paraclinical aspects of brucellosis with and without neurological manifestations. Data of 30 patients, 15 cases with nervous system involvement (neurobrucellosis) and 15 cases without neurological complication (brucellosis) were collected and analysed. Constitutional manifestations of the disease including: fever, headache, fatigue, anorexia, diaphoresis, arthralgia and low back pains were detected with nearly the same frequencies in both groups. Exceptions were headache which was more common in patients with neurobrucellosis (73% vs. 33%) and arthralgia which was detected more frequently in cases with brucellosis than neurobrucellosis (53% vs. 13%). Signs and symptoms of meningeal irritation and disturbances of consciousness were the most common manifestations in cases with neurobrullosis, which had been detected in 60% and 46.7% of cases respectively. Less common neurological presentations, in decreasing order of frequency were ophthalmoplegia, papilledema and seizures (each in 26.7% of cases), spastic weakness of limbs (20%), hearing loss (13.3%) and spinal epidural abscess (6.7%). Two of our patients with neurobrucellosis had negative serum and CSF agglutinin test, in whom diagnosis was made by blood and CSF cultures. In patients with neurobrucellosis, MRI of brain and spinal cord showed abnormalities in 5/15(33.3%) of cases, including decreased lateral ventricular volume due to brain swelling (2/15), hydrocephalus with periventricular edema and meningeal enhancement in posterior fossa (1/15), multiple hypodense periventricular lesions, ischemic or demyelinative in nature (1/15) and spinal epidural abscess (1/15).

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INTRODUCTION

Brucellosis is a zoonotic illness with a prevalence of 60 to 80/100,000 in Mediterranean and most Middle Eastern countries. Iran has a disease incidence of 132/100000. Hippocrates may have described it in his treatises “on epidemic” (1, 2). Some occupations have been identified to be at an increased risk (3). In recent decades the risk factors for infection have shifted from occupational hazards to the consumption of contaminated food, especially milk and cheese (4). Human - to - human transmission is rare and its infectiousness by the aerosol route (5) makes it a potential for bioterrorism

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and transmission in laboratories (6-9). Reticulo-endothelial cells of animals are a favored location for organisms and are the chief site of infection in humans, especially macrophages. Humans that remain chronically infected usually harbor Brucella organisms in their lymphatic/ reticuloendothelial system. Bones and joints are the organ systems next most likely to remain chronically infected (10-16). Neurological manifestations of acute brucellosis (irritability, lethargy, headache, anorexia, inattentiveness, mood and sleep disturbances) are not conventionly termed neurobrucellosis. Neurobrucellosis can develop at any stage during acute or chronic disease, and may present as acute or chronic meningoencephalitis, radiaculitis, polyradiculoneuropathy (GBS), acute demyelinating disease (ADEM) (17-19), myelitis, spinal epidural and multiple cerebral or cerebellar abscesses, ruptured mycotic aneurysms, sciatica, myositis, papillitis, papilledema, retrobulbar neuritis, optic atrophy , cranial nerve lesions (ophthalmoplegia due to III, IV and VI nerves involvement) and hearing loss (20). In regions wherein B.melitensis is endemic, brucellosis may be the most common cause of acquired hearing loss. Two of our patients had hearing loss which correlates to the above treatise.

Central nervous system involvement occurs in 5-7% of all cases, but evidence for focal dysfunction of the nervous system (peripheral and central) is reported in 5-10% of chronic brucellosis which is properly termed neurobrucellosis (21-23). Peripheral neuropathy alone is rarely associated with neurobrucellosis. Lumber vertebral body and disk granulomata resulting in extra axial compression, weight bearing joint involvement, degeneration of anterior horn cells, as well as ascending and descending tracts, inflammatory involvement of cauda equina and chronic arachnoiditis (24) are other features of neurobrucellosis, which usually are responsive to therapy. Most physicians rely on SAT for diagnosis (25), but PCR is more sensitive and specific (26,27). HIV infection dose not seem to affect the accuracy of anti- Brucella antibody detection (by ELISA), clinical course and treatment (28). CSF shows invariably pleocytosis and increased protein. Glucose may be normal or decreased. Blood cultures have very variable sensitivity (53 to 90%) (29). In patients with negative blood culture and a high clinical suspicion of brucellosis, bone marrow biopsy and culture are advisable, as it has a sensivity in excess of 90%, and cultures may be positive even when the patient has been treated with antibiotics (30).

MATERIAL AND METHODS

This prospective descriptive cross- sectional study was carried out in thirty patients, (15 without CNS complication and 15 with neurobrucellosis) to evaluate clinical, epidemiological, serological and imaging aspects, within 2002-2005. Inclusion criteria for brucellosis were considered 1) Clinical features 2) Positive serology (wright $\geq$ 1:160, Coomb's test $\geq$ 1:320, 2ME $\geq$ 1:80) or positive blood or bone marrow cultures. Inclusion criteria for definite diagnosis of neurebrucellosis were 1) neurological dysfunctions, not explained by other diseases, 2)abnormal cerebrospinal fluid, indicating lymphocytic pleocytosis and increased protein, 3) positive IgG agglutination titer in the blood (SAT) and CSF, 4)response to specific therapy with significant drop in the CSF lymphocyte and protein concentration. All patients underwent physico-neurological examination and blood analysis for CBC, CRP, ESR and SAT. Blood culture (Bactec method) was performed in all cases, but CSF culture was performed only in those who had negative blood culture and also negative serum and CSF agglutinin test (because the positive rate reported was only in about 30% of cases with neurobrucellosis). All patients with neurobrucellosis underwent brain and / or spinal MRI with and without gadelinium injection and CSF analysis. We used doxycycline 100 mg twice daily and rifampicin 600-900 mg once daily (both orally) for a minimum of eight weeks, and streptomycin one gram per day for initial fourteen days as a common therapeutic regimen. All patients were followed every month for up to 6 months under the supervision of an experienced infections disease specialist.

CSF analysis was performed again 2 months after treatment. All data were analysed by SPSS and using Fisher's exact X^2 test.

Table 1. Epidemiological data of patients with brucellosis and neurobrucellosis

Parameters	Brucellosis (15)	Neurobrucellosis (15)	P.Value
Age- range (years) Mean ± S.d	15-67 37.7 ± 19.9	15-50 27 ± 11.6	0.220
Male/Female	9/6	9/6	-
Urban/ rural	5/10	6/9	0.705
Animal contact and milk product consumption	12(80%)	14(93.3%)	0.598

RESULTS

The age of the patients without nervous system involvement and with neurobrucellosis ranged from 15-67 and 15-50 years respectively. The male to female ratio was the same (9/6) in both groups, and there was no meaningful difference in being urban or rural, having had animal contact or having had dietary exposure to milk products (Table 1).

Fever, headache, fatigue, anorexia, diaphoresis and low back pains were detected with nearly the same frequencies in both groups.

The only exceptions were headache which was more common in patients with neurobrucellosis (73% vs. 33%, P: 0.028) and arthralgia which was detected more frequently in cases with brucellosis than neurobrucellosis (53% vs 13%, P:0.025) (Table 2). Neurological symptoms and signs of cases with neurobrucellosis, in order of decreasing frequency, were meningeal irritation (60%) , altered or decreased level of consciousness (46.7%). Papilledema, convulsion and ophthalmoplegia (each being 26.7%), spastic weakness of limbs (20%), hearing loss (13.3%) and epidural abscess (6.7%). Meningoencephalitis (50%), meningitis (40%) and cranial nerve palsies (26%) were the most common clinical presentations. The less common manifest-tations were meningism, raised ICP, pyramidal syndrome and cord compression (Table 3). Para-clinical data had also been similar in both groups. Two of our cases with neurobrucellosis had negative blood culture and also negative agglutinin test in the blood and CSF samples, in whom diagnosis was made by CSF culture. Brucella melitensis was the causative agent in all of positive cultures. Decreased volume of lateral ventricles due to brain swelling (2/15), hydrocephalus induced by basilar arachnoiditis and meningeal inflammation (enhancement with gadolinium) (1/5), small multiple hypodense lesions either demyelinative or ischemic (1/15) and spinal epidural abscess (1/5) were found in MRI of patients with neurobrucellosis.

Table 2. Frequency of constitutional symptoms and signs

Parameters	Brucellosis No. (%)	Neurobrucellosis No. (%)	*P* Value
Fever	5(33.3)	8(53.3)	0.269
Headache	5(33.3)	11(73.3)	0.028
Fatigue	12(80)	11(73.3)	0.50
Anorexia	13(86.7)	12(80)	0.50
Myalgia	2(13.3)	3(20)	0.143
Arthralgia	8(53.3)	2(13.3)	0.025
Low back pain	6(40)	3(20)	0.213
Lymphadenopathy	2(13)	-	-

Table 3. Frequency of neurological symptoms and clinical manifestations in cases with neurobrucellosis

Symptoms and signs		Manifestations	
S. signs	**No (%)**	**Manifestations**	**No (%)**
Meningeal irritation	9(60)	Meningoencophalitis	8(53)
Consciousness disturbance, Confusion	7(46.7)	Meningitis,	6(40)
Pipilledema	4(26)	Cranial n. palsies	4(26.7)
Convulsion	4(26.7)	Meningism	3(20)
Ophthalmoplegia	4(26.7)	Raised – ICP	3(20)
Spastic paresia	4(26.7)	Pyramidal syndrome	3(20)
Hearing loss	3(20)	Cord compression	1(6.7)
	2(13.3)		

Most patients with brucellosis without neurologic involvement had generalized or diffuse form of the disease, without localization. There were also cases of spondylitis (three being lumbosacral and one cervical), arthritis (two cases), endocarditis and epidedymoorchitis (each being one case).

DISCUSSION

Patients with brucellosis suffer from a range of signs and symptoms (31). The nervous system involvement can be categorized into central and peripheral forms. The former is usually acute and presents as meningoencephalitils, while the latter may either be acute or chronic in presentation. The peripheral nervous system involvement often presents itself as polyradiaulopathy and less commonly as cauda equina like syndromes and peripheral neuritis (32). All case of CNS involvement, appear to be complicated by meningitis at some stage. For unclear reason< 50% of patients with documented meningitis will have meningeal signs or symptoms, but in our study meningeal irritation and meningoencephalitis were the most common neurological manifestations.

The effect of the disease on the nervous system can be due to direct effect of bacilli, cytokines or endotoxin on brain, meninges or peripheral nerves. It can also be secondary to the bone disease or abscess formation in the brain and spinal cord. One of our patients which had cord compression due to lumbar epidural abscess. Brucella endotoxin can cause vascular and perivascular inflammation. In this study MRI of one of the patients showed multiple small hypodense lesions without enhancement, which could be demyelinative or ischemic in nature. Neurobrucellosis may develop at any stage of the disease (33), but in our study nearly all of the cases were in subacute or chronic phases of infection. Chronic meningitis and neuronal involvement have also been reported (34-35). One of our patients showed basilar meningeal enhancement (inflammation) with hydrocephalus in the brain MRI.

The infection may trigger an immune mechanism leading to demylination (GBS and ADEM). Myeloradiculopathy which can result from infection has also been reported (36).Cases of neurobrucellosis with spinal abnormality, closely resemble CNS tuberculosis but neurobrucellosis seldom cause communicating hydrocephalus, despite very high levels of CSF protein; and unlike those with T.B meningitis, there is a high risk for hearing loss (Robert Rus and et all).

Combination of potential exposure, consistent clinical features and significantly raised level of Brucella agglutinin (with or without positive cultures of blood, body fluid or tissues) confirm the diagnosis of acute brucellosis.

The traditional gold standard of diagnostic testing is the serum agglutination test (SAT), which measures both IgG and IgM antibodies of Brucella melitensis, abortus and suis, but not canis. Although IgM titers are the first to rise after infection, but paradoxically remain elevated longer than IgG; thus, measures of IgG are used to monitor effectiveness of therapy. 2-Mercaptoethanol inactivates IgM

antibodies and allows agglutination only by IgG. A high titer of IgM suggests recent exposure, while a high titer of IgG indicates active disease. Lower titers of IgG may suggest past exposure or treated infection.

The prozone phenomenon may cause false – negative result. Infection with cholera, tularemia and Yersinia can result in false – positive reaction. An indirect coombs test has been developed to look for the presence of non-agglutinating anti – abortus antibody. Enzyme linked Immunoabsorbent Assay (ELISA) is more sensitive in the detection of B. antibody than SAT. Most clinicians rely on the SAT for diagnosis and treatment of brucellosis, using the coombs and ELISA primarily in patients having negative SAT, but with a high likelihood of having brucellosis. Polymerase chain reaction (PCR) is highly sensitive and specific, but not yet commercially available. Detection of elevated levels of antibody in the absence of clinical symptoms is common in endemic areas. To stablish a diagnosis in these cases clinical and serological evaluation should be repeated after 2-4 weeks and a further risk in titer sought.

Most authorities consider agglutination test titers of 1: 160 or higher to be significant in symptomatic patients, living in a non- endemic area. However in epidemic areas, only titers of 1:320 or higher should be considered important (39). The minimum titer required for the confirmation of the diagnosis is 1:160 (38-39). All of our cases had titers more than 1:160.

The purpose of our attention to brucellosis and reporting these cases are 1) to create awareness and highlight the fact that brucellosis should be kept in mind in patients with neurological presentations. 2) To advise the concerned medical authorities to pay special attention to this infectious problem. 3) Finally to mention the issue that, complete treatment of brucellosis on time, usually reverses most neurological symptoms, although some cases would have permanent deficits, particularly if myelopalthy is present.

Conflict of interests

We have no conflict of interests.

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