Research Article

Neurobrucellosis: Antimicrobial Treatment of Six Complicated Cases of Brucellosis

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Abstract

Brucellosis is a classical zoonosis; it is a common disease in the Middle East countries. Involvement of the Central Nervous System by *Brucella* microorganisms might be not uncommon and is parallel to the prevalence rate of the disease among population. The work reported here is for six cases with brucella meningoencephalitis diagnosed by isolation of *Brucella* microorganisms from their blood and spinal fluid together, with high anti-brucella antibodies in their blood and Cerebro Spinal Fluid (CSF). Cases of PUO admitted to Fever Hospital and Neurological unit in the Medical City Teaching Hospital were evaluated clinically and neurologically. Six cases (three males and three females) suspected of neurological involvement by the disease all had fever, sweating +/- joint pains, all had meningeal irritation signs, abnormal CSF findings and all had history of raw milk &/or cheese consumption. They all were treated by different courses of many antibiotics for different times with skeptical responses. The general complaint was varying between fever, vomiting, weight loss, severe depression, headache and sweating, one case had change of sensorium, and hearing loss, one had cranial nerve palsy and three had peripheral weakness. All the cases had pleocytic CSF changes and *Br. melitensis* types 2 and 3 and *Br. abortus* type 4 isolated from their blood and all but one had same Brucellae isolated from their CSF. All cases had high titers of anti-brucella antibodies raised both in the serum and CSF though the Rose Bengal and ELISA tests. The treatment given was different of two or three combinations of Rifampin, Tetracycline, Cefotaxim, and Streptomycin for eight weeks up to four months for those with lumber osteomyelitis and epidural abscess cases. The outcome of cases was satisfying; four cases were cured without sequale, one case with cerebral abscesses was died and one case developed hearing loss and peripheral nerve weakness. It can be concluded neurobrucellosis is a treatable disease with a favorable outcomeexcept when there is a myelopathy or deafness and careful awareness of the disease as it is not an uncommon complication of common and treatable disease in our community is required.

Key words: ***Brucella, brucellosis, brain, meningitis, neurobrucellosis***

INTRODUCTION

Brucellosis, also called Gibraltar fever, Malta fever, Mediterranean fever, or undulant fever, is a classical zoonosis caused by ingestion of unsterilized milk, milk products, or meat from infected animals or close contact with their secretions. [1, 2] Brucella spp. is function as facultative intracellular parasites causing chronic disease, which might persists for long time. Symptoms of the disease include fever, profuse sweating, joint and muscle pains, and many other constitutional symptoms. It is a multisystem infection that can involve almost any organ system and may present with a broad spectrum of clinical presentations. Neurobrucellosis is a serious complication of brucellosis. [3-9] It occurs in less than 5% of patients however, (5-10%, even20% has been reported), [2, 9] and usually presents as acute or chronic meningitis in patients with brucellosis [3-6]. The clinical features of neurobrucellosis can vary greatly and, in general, tend to be chronic. Many of the laboratory procedures employed in the diagnosis of brucellosis are frequently give negative results.[3, 8, 9- 12] Neurologic manifestations of brucellosis according to many authors' experts in the CNS infection include: meningitis, encephalitis, myelitis, and radiculoneuritis, intracerebral abscesses, epidural abscess, demyelination and meningovascular syndromes. [7-9, 10-17] Cranial nerve involvement might be rare so as other complications e.g. spinal abscess, *Guillain Barre* Syndrome, intracranial

hypertension and others [18-21]. Neuromuscular weakness and hearing loss are chronic irreversible complications.[10, 16, 22] There are three types of imaging abnormalities seen in neurobrucellosis:inflammation, white matter changes, and vascular insult. However, Clinical-radiologic correlation in neurobrucellosis varies from a normal imaging study despite positive clinical findings, to a variety of imaging abnormalities that reflect either an inflammatory process, an immune-mediated process, or a vascular insult.[5] Inflammationmay cause granulomatous formation or enhancement ofthe meninges, perivascular space, or lumbarnerve roots [5, 10-12], (Figures 1 &2). For these reasons, and because brucellosis is a disease, which is both treatable and curable, the degree of suspicion should be high, especially in endemic areas, so that an early diagnosis of neurobrucellosis can be made to allow suitable treatment to be established.

There is no general consensus about the best way of combination of antimicrobials to be given [3-8, 23-28] so as for how long the time should be. The choice of treatment of meningitis should include antibiotics that can pass the blood - brain barrier and then better to be of the bactericidal group. The Tetracycline's in all their forms are bacteriostatic; they can deal better with an intracellular microorganism as *Brucella.* Rifampicin is bactericidal and its combination with the tetracycline is synergistic in effect, it passes easily the blood-brain barriers. Similar action of the Rifampicin is in its combination with the other antituberculous treatment [24-27]. Both the Tetracycline and the Rifampicin are preventing the protein biosynthesis by the bacterium. One of the amino glycosides might be included in the therapy of neurobrucellosis as Streptomycin or Gentamycin but they are scarcely passing the blood – CSF barrier. The third generations Cephalosporin's as Cefotaxim or Ceftriaxone are preventing cell wall synthesis of the bacterium, they are bactericidal agents and can be used affectively when the above combinations are contraindicated as in pregnancy. The Co-Trimoxazole as an antifolate agent that causes blockade of specific stages in intermediary metabolism, and the aminoquinolones which are blocking the protein biosynthesis are also affective in treatment of uncomplicated brucellosis but not much used in neurobrucellosis. [3, 29] The work reported here is for six cases of neurobrucellosis admitted to the Fever Hospital and the Medical City Teaching Hospital in Baghdad for the time between the years 1990-2006 and they were fulfilled all the criteria mentioned above.[23]

PATIENTS AND METHODS

Diagnosis of neurobrucellosis usually requires satisfaction of the following criteria: Clinical features of the illness compatible with a known neurobrucellosis syndrome, typical CSF changes (pleocytosis, elevated protein concentration), positive results of either CSF culture or appropriate serological tests (e.g. IgG agglutination testing titers of >1:160 in CSF or >1:320 in blood), Clinical improvement as well as improvement in CSF pleocytosis and fall in CSF and blood anti *Brucella antibody* titers after an appropriate treatment given, and an inability to prove a more suitable alternative diagnosis.[3, 10, 13-17]

Cases of PUO admitted to the Fever Hospital and Neurological unit in the Medical City Teaching Hospital in Baghdad for the time between the years 1990 and 2006 were evaluated clinically and neurologically for involvement of the central nervous system (CNS) by the disease.

Six cases admitted (three men and three women), their age ranged between 19 and 58 years, and were suspected of having neurological involvement by *Brucella* infection. They had possessed the following criteria: All had fever, sweating +/- joint pains, meningeal irritation signs, abnormal CSF findings and all had history of raw milk &/or cheese consumption. All the cases were treated by different types of antimicrobials singly or in a combination forms and for different times between one and six months without improvement.

RESULT

The case profile of presentation is explained in Table 1. Constitutional symptoms of fever, myalgia, arthralgia, anorexia depression and weight loss were the chief complaints. One of the female patients was pregnant in the second trimenister, three cases had peripheral nerve involvement, 6th cranial nerve palsy was present in one case, one patient had multiple brain abscesses seen by MRI, with hearing loss and impaired consciousness. All cases had isolation and typing of *Brucellae* from their blood and all but one had isolation of *Brucellae* from their CSF fluid (Table2). The isolate were *Br. melitensis* types 2 and 3 from four patients, the other two isolate were *Br. abortus* type 4. Different types of serological tests (Rose Bengal, ELISA, Indirect Coombs test, and 6 Mercaptoethanol) were employed for testing the serum and the CSF of the patients. The results of anti brucella antibody titers were high in both the serum and CSF samples (1/320-1/1280).The CSF examination is shown in Table 3, it reveals pleocytic changes among all cases with lymphocytic profile, high protein and normal or moderately lowered sugar. The treatment given was Doxcycline 100 mg+ Rifampicin 450 mg bd for 8/52 + Streptomycin 750 mg IM for first 2/52; cases 4&6 had

lumbar 3rd and 4th vertebrae osteomyelitis and epidural abscess, their treatment was extended for further month. Cefotaxime 100mg/Kg+ Rifampicin were the treatment given for Case 2 (pregnant woman). All cases had Steroids given for the first 3 days, together with supportive measures and watch up for 3 months for recovery. The outcome was favorable; four patients had full improvement without sequel. Patient no.3 died because of multiple *Brucella* brain abscesses. Patient no.6 was remained with significant hearing loss, peripheral weakness and mild urinary retention.

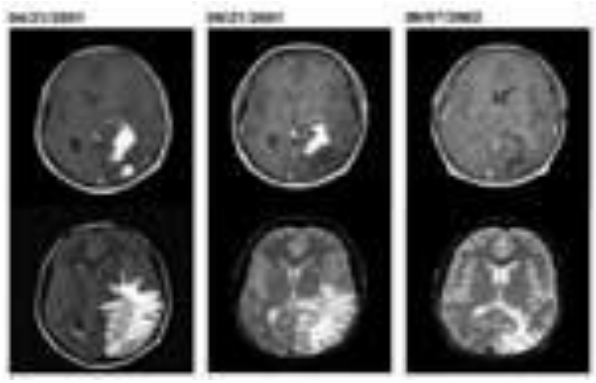

Figure (1): Radiological images in Neurobrucellosis: brain edema and atrophy.

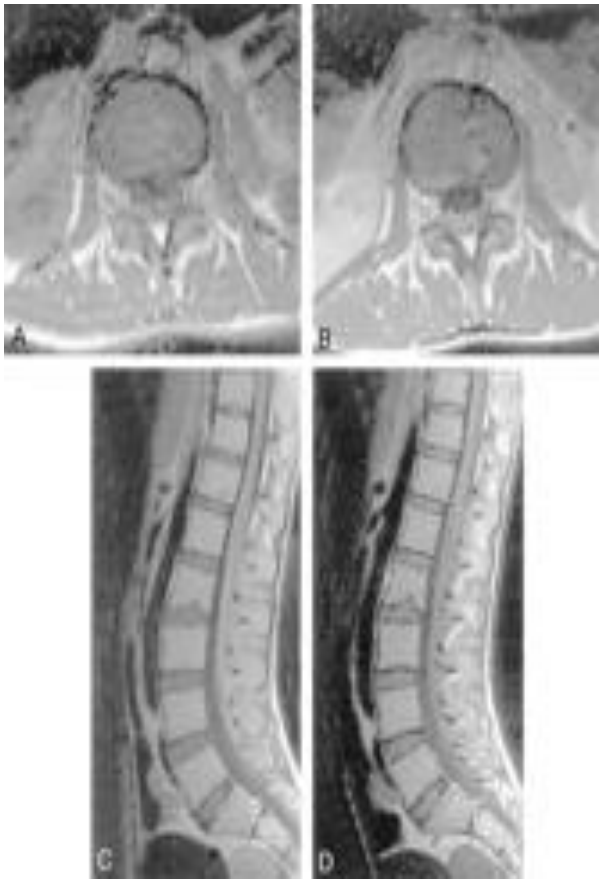

Figure (2):Lumber injection of a gadolinium-based contrast agent show enhancement of the lumbar nerve root.

Table (1) Clinical presentation of Cases of Neurobrucellosis

Case 1 F 19 years	*Complaints Fever, vomiting, weight loss, sever depression*	*Duration 6 months*	*History of treatment Yes, different antibiotics, ECT shock*
Case 2 F 37 Years	***Fever, vomiting, headache, sweating***	***5 weeks***	***Yes, different***
Case 3 M 53 Years	***Fever, hearing loss, vomiting, change of sensorium***	***4 weeks***	***Ampicillin, COT***
Case 4 M 48 Years	***Peripheral weakness, backache, fever, sweating***	***3 months***	***Analgesics, COT, Gentamycin***
Case 5 F 21 Years	***Fever, fits, left sided weakness, 6Th CN palsy, loss of weight***	***6 weeks***	***Different antibiotics, antiepileptic***
Case 6 M 58 Years	***Peripheral weakness, hearing loss, sever backache, burning urine***	***3 months***	***Analgesics, keflex doxycycline***

Table (2) Laboratory findings of cases of neurobrucellosis

Cases	*Blood culture*	*Blood serology*	*CSF culture*	*CSF serology*
Case 1	***Br. Melitensis, type 2***	***RB, 1/ 640 Indirect Coomb,s 1/160 MTG, 1/320***	***Br. Melitensis, type 2***	***RB, 1/160 Indirect Coombs 1/80***
Case 2	***Br. Abortus, type 4***	***RB, 1/1280 Coomb,s +***	***Br. Abortus, type 4***	***RB, 1/320***
Case 3	***Br. Melitensis, type 2***	***RB, 1/640, ELISA, 1/ 320***	***Br. Melitensis, type 2***	***RB, 1/ 320, ELISA, 1/320***
Case 4	***Br. Melitensis, type 2***	***RB, I/640 ELISA 1/320***	***Negative***	***RB, 1/ 160 ELISA, 1/160***
Case 5	***Br. Abortus, type 4***	***RB, 1/ 640, ELISA, 1/ 640***	***Br. Abortus, type 4***	***RB, 1/ 160 ELISA, 1/ 320***
Case 6	***Br. Melitensis, type 3***	***RB, 1/ 1280 MTG, 1/ 320***	***Br. Melitensis***	***RB, 1/ 320***

Table (3) The CSF findings of cases of neurobrucellosis

Cases	*Cells/ Cmm*	*Types*	*Protein mg/ Dl*	*Glucose mg/ Dl*
Case 1	*388*	*L 84% PMN 16%*	*294*	*38*
Case 2	*224*	*L 68% PMN 32%*	*224*	*44*
Case 3	*360*	*L 78% PMN 22%*	*340*	*58*
Case 4	*492*	*L 95% PMN 5%*	*156*	*54*
Case 5	*580*	*L 80% PMN20%*	*320*	*32*
Case 6	*84*	*L 100%*	*212*	*68*

DISCUSSION

Neurobrucellosis does not always correlate with the clinical picture of the disease which is common in our community; it needs high rate of suspicion. In Iraq, I have the honor to diagnose the first case of neurobrucellosis in our country.[14] Ever since we started to diagnose more cases of neurobrucellosis among our meningitis cases admitted the fever hospital or the neurological units. Many authors in the Middle East and other areas have good profiles on neurobrucellosis. [2, 3, 5-9, 12, 14, 22, 23, 25]

The occurrence of neurobrucellosis during the acute phase of illness may be due to direct deleterious effects of organisms invading nervous tissues, to the release of circulating endotoxins, or to the immunologic and inflammatory reactions of the host to the presence of these organisms within the nervous system or within other tissues of the body.[1, 3, 8, 13]

Sometimes, neurologic findings may be the only signs of brucellosis.[16, 17, 23]; the most common

Presentation of neurobrucellosis is acute or chronic meningitis.[3-6, 24]

There are frequent reports of brucellosis from countries such as Kuwait, Saudi Arabia, Iran, Iraq and other

Countries of the Eastern Mediterranean Region.[2, 3, 5-9, 12, 14, 22-24]

There was wide range of clinical presentation of our cases in this report from acute to sub acute meningitis followed by peripheral weakness, then hearing loss and change in the level of consciousness. This was associated with the classical trait of fever, vomiting and headache that accompany infection of the meninges.

Haji-Abdolbagi and his associates, 2008 had postulated in their analysis for31 cases of neurobrucellosis in Iran between 1990-2004;meningitis and meningoencephalitis were the most common form of neurobrucellosis among their patients.3 MRI showed hydrocephalus in two patients, brain abscess in one, and epidural abscess in one, the abscess drainage revealed positive culture for *Brucella*.

The most commonly-used antibiotics were combinations of Rifampin, Doxycycline and Trimethoprim-Sulfamethoxazole. Cefotaxim, Ceftriaxone, Streptomycin and Gentamycin were also used in the treatment and for different courses.[3-7, 12, 16, 19, 25-28] The Doxycycline is long acting tetracycline, it is effective and can be given twice daily in a dose of 100 mgeach. The Rifampicin is used in a dose of 450 mg bd is effective and tolerable but it needs watching up the liver function tests as it is an enzyme inducer and might cause clinical hepatocellular jaundice. The amino glycosides are synergistic in the combinations and can be used only in the first two weeks of treatment to prevent renal and auto toxicity. Perhaps, the Aminoquinolones and the C0-Trimoxazole are less used for treatment of neurobrucellosis than the classical treatment of combination of the Rifampicin and Doxycyclin.[3, 26, 29]

All the above mentioned drugs were effective and curable when used early in the infection in any combinations.[3-14, 16, 17, 22-29]

While we treated our uncomplicated patients for two months, but with addition of further one month for complicated cases with osteomyelitis; this showed an optimum treatment, relapse was not observed in six to 12 months of follow-up. However, others suggested treatment is to continue for 4-6 months.[3]

One of our cases had sixth cranial nerve palsy that improved after treatment. Patients with acute infection can have cranial nerve palsies that usually resolve completely with administration of antibiotics, whereas those with chronic CNS infection often have permanent neurologic deficits.[7, 12, 16]

The syndrome of parenchymatous dysfunction can occur at any Point in the CNS but it most commonly affects the cerebellum, spinal cord, and cerebral white matter.[3, 5-7, 19, 21]

Meningovascular complications, in particular mycotic aneurysms, ischemic strokes, and subarachnoid hemorrhage, are relatively common.[6, 7, 28] but were not seen among our cases.

Permanent neurologic deficits, particularly deafness, are common.[10, 16, 22] in the chronic forms, immune mediated demyelination has been proposed also.[10, 26]

Of 1375 patients with brucellosis admitted to the infectious diseases ward of a tertiary hospital in Iran, there were 20 cases had CNS involvement. A 12 had meningitis (acute and sub acute), 4 had meningoencephalitis, 2 with myelopathy, 1 had polyradiculopathy and 1 had meningovascular complications.[12]

Bellissma et al. reported 6 cases of neurobrucellosis in Italy, of them, 2 had meningoencephalitis, one had meningitis with brain abscess and 3 had encephalomyelitis.[27]

In another study in France by Koussa et al for 15 patients with neurobrucellosis, two of them had polyradiculoneuritis.[28] Pleocytic CSF changes of raised protein, lymphocytic cells and lowered sugar levels are common and in agreement with our findings.[3, 6-10, 28] Microbial isolation from the CSF is not wide in many of these reports, while positive serology and raised anti brucella antibodies in the spinal fluid are common.[12, 22, 25, 27.]

In conclusion, Neurobrucellosis showed wide range of clinical presentation, it was a treatable disease with a favorable outcomeexcept when there is a myelopathy or deafness. Imaging abnormalitiesin neurobrucellosis are variable and may mimic other infectiousor inflammatory conditions. Imaging appearance reflectsinflammatory, demylinatin or a vascular insult, it does not always correlate with the clinical picture.

The author recommendation is that careful awareness of neurobrucellosis in Iraq is required as it is not an uncommon complication of common and treatable disease.

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