**Neurobrucellosis in Northern Iraq**

A study of clinical characters and outcome in 16 patients with neurobrucellosis in Nineveh Governorate

*Ismail D. Saeed*   **Mohammad M. Fathi**

* M.B.Ch.B, C.A.B.M, Department of Medicine – College of Medicine – University of Mosul. Mosul – Iraq
** M.B.Ch.B, F.I.C.M.S, Department of Medicine – College of Medicine – University of Mosul. Mosul – Iraq

**Abstract**

Neurobrucellosis is a rare neurological complication of brucellosis. This study describes 16 patients of neurobrucellosis which undoubtedly account for a small percentage of total admitted cases of brucellosis to Mosul city hospitals for tertiary care over a period of five years. The diagnosis was depended on history, clinical examination, positive brucella test, CSF examination and MRI or CT of the brain or spine. Headache, fever, sweating fatigue, drowsiness, neck stiffness, symptoms of cranial nerve involvement and backache were the common clinical features. Cerebrospinal fluid (CSF) showed an abnormal finding regarding increased cell count, elevated protein levels and low glucose in 9 patients and positive serology in 13 patients; while blood serology was highly reactive in all. The patients received a combination antibiotic therapy for 3 – 6 months. Patients with acute neurological complications as well as those with radiculoneuropathy responded favourably to treatment. The outcome was as follow: Eight patients recovered completely while other eight patients left with partial or complete disabilities. As neurobrucellosis is a fatal condition if remained untreated; doctors especially in endemic areas like Iraq should consider the likelihood of neurobrucellosis in patients with unexplained neurological and psychiatric symptoms.

**Key words**: brucellosis, neurobrucellosis, brucellosis in Iraq.

**Introduction**

Brucellosis an intracellular bacterial infection (1) is considered by Food and Agriculture Organization (FAO) and the World Health Organization (WHO) as one of the most widespread zoonotic diseases in the world (2). It is an endemic disease in Iraq and many other countries over the world (3,4). The principle animal reservoirs for brucellosis in order of frequency in Iraq are infected sheep, goats (B. melitensis) responsible for more severe and acute type of brucellosis, cattle (B. abortus) responsible for milder but more prolonged infection (5) and in some areas buffalo and camels may be responsible (6). It infects all age groups including children, young, middle aged and elderlies (7). Although occupational exposure and direct contact with infected tissues, blood, urine, vaginal discharges, aborted foetuses or placentas can transmit brucellosis (6,8), the most common and important route for disease acquisition in Iraq and possibly in other endemic areas is through ingestion of unpasteurized dairy products using raw infected milk.

A type of soft cheese in Mosul and in Iraq as a whole, prepared from raw milk at home is commonly consumed by people as delicious breakfast and in many occasions it is highly infected with brucella bacilli principally due to lack of regular campaigns of livestock vaccination in Iraq in addition to sanitary, socioeconomic, and political reasons (6). Neurobrucellosis is one of the most serious complications of brucellosis (3); a complication which present with different neuropsychiatric manifestations and may be fatal if not detected and treated early (6,7). Neurological complications of brucellosis involve both the central (CNS) or peripheral nervous system (PNS) (4,10). Involvement of the central nervous system (CNS) in brucellosis is a rare event and according to literatures it is present in less than 5% of cases, predominantly with B. Melitensis,
but if headache, irritability, and other constitutional symptoms found in acute brucellosis were included, the prevalence would be much higher\textsuperscript{(9,10,11)}.

The clinical presentation of brucellosis localized to CNS is diverse and localized forms are difficult to diagnose\textsuperscript{(9)}. Here we describe different characters of 16 patients with diagnosis of neurobrucellosis.

**Design and setting:** case series and case reporting of 16 patients of neurobrucellosis in 3 major hospitals in Mosul city (Ibn Sena Teaching Hospital, Al-Salam Teaching Hospital and Al-Zahrawi Teaching Hospital).

**Patients and methods**

During 5 years period (2007-2012) a diagnosis of neurobrucellosis was confirmed in 16 patients admitted to 3 hospitals (Ibn Sina Teaching Hospital, Al-Salam Hospital and Al-Zahrawi Private Hospital) in Mosul for tertiary care. Their ages ranged between (18-65) years with a mean ± SD (28.18±14.28) and consisted of 7 male and 9 female patients. They were equally distributed between rural and urban areas.

In addition to demographic features, the data collection comprised of other important parameters which are: History of recent exposure to a known or possible source of brucellosis especially cattle, sheep, goats and/or consumption of raw or inadequately cooked milk or milk products, clinical features compatible with neurobrucellosis, laboratory data, which included Rose Bengal, tube (wright) agglutination tests and 2-mercaptoethanol agglutination test titer (2ME) for brucella; both in blood and cerebrospinal fluid (CSF). A blood titer of >1/160 was considered significant while any positive titer in cerebrospinal fluid (CSF) was considered significant. The enzyme-linked immunosorbent assay (ELISA), was available only for some patient. Blood culture was not performed for reasons that will be discussed latter. A lumbar puncture with CSF examination and additional blood tests for haemoglobin, white blood cell count and ESR were performed for all patients. Nerve conduction study and audiometry study were done for some selected cases. Neuroimaging examination, in which the patients were submitted to magnetic resonance imagining (MRI) or computed tomography (CT) of the brain or spine, was an additional criterion. X-ray of lumber spine was the initial imaging investigation for those who suffered from significant backache. The exclusion of other important neurological diseases was considered seriously as neurobrucellosis may simulate many such diseases.

Treatment details was also taken in consideration: 14 patients were given an average daily doses of 200mg doxycycline and 600-900mg rifampicin orally in divided doses according to patient's body weight. Two patients were given an additional therapy with ceftriaxone 2gm/day (triple therapy). Other non-antibiotic medications like steroid and antiepileptic drugs were added according to specific needs of the patient. To detect patient’s response, drug side effects and cases of early relapses, all patients are regularly observed and followed for the first 3 months of therapy initiation and instructed to report any new symptoms.

**Results**

The important characters of 16 patients with neurobrucellosis, 7 males and 9 female with ages ranged (18-65) years and mean ± SD (28.18±14.28) were studied among patients who admitted to Mosul hospitals with diagnosis of neurobrucellosis.

In addition to those toxic febrile neuropsychiatric manifestations related to the acute-febrile phase of the brucellosis, neurobrucellosis were involved several areas of the central and peripheral nervous systems and developed during acute, subacute and chronic stages of the disease. The most common forms of presentations in our series were as follow in decreasing frequency: Seven cases of acute or
chronic cranial nerve involvement (one with optic nerve involvement and six with either unilateral or bilateral vestibulocauditory nerve involvement), five cases with acute or subacute meningitis or meningoencephalitis, three cases with subacute or chronic polyradiculoneuropathy, and one case with myelitis or myelopathy. Other forms of neurobrucellosis were not present. General features included fever, sweating, malaise, fatigue, backache, arthralgia, nausea, anorexia, etc. In cranial nerve forms the patients presented with either visual changes or sensorineural deafness and vertigo, according to whether optic or vestibulocauditory nerve(s) were involved. All cases of meningitis or meningoencephalitis preceded by fever, severe headache, drowsiness, vomiting, generalized body aches, malaise and epileptic fits in one patient. In polyradiculoneuropathy form the patients presented with backache, unilateral or bilateral sensory and/or motor changes in one or both lower limbs. The single case of myelitis was presented with spastic paraplegia. Sphincter disorders observed in one patient. The duration of illness was ranged between 10 days and 6 weeks in 7 patients. While in the other 9 patients their illnesses were prolonged or recurred and ranged between 2 months to 3 years.

Nearly all patients acquired the disease from ingestion of contaminated and unpasteurized milk or milk products, although direct contact with animals and other animal products was observed in 3 patients in addition. The rose Bengal test was positive in all patients and brucella agglutination test (BAT) with 2ME test (regardless to species of brucellosis) ranged from 1/320 – 1/1280 in blood. CSF serology was positive in 13 patients, Other CSF findings were as follow: Nine patients showed abnormal CSF finding including high pressure, lymphocytic pleocytosis, high protein and normal or low sugar, while seven patients showed normal CSF pressure, cellularity, protein and sugar. Brain MRI or CT scan was normal in nine patients, while in three patients showed brain oedema and in another 3 patients showed evidence of diskitis and/or spinal root(s) enhancement. In one patient the finding was compatible with myelitis.

The medications are well tolerated and no one discontinue the treatment. Patients with acute neurological complications as well as those with radiculoneuropathy responded favourably to treatment. The duration of treatment ranged between 3 – 6 months.

The outcome:
Fever and other general symptoms of brucellosis were improved within 10 – 20 days of antibiotic therapy. Eight patients were recovered completely, especially those with acute neurological complications and radiculoneuropathy. The remaining eight patients also recovered but left with residual neurological deficits especially those with cranial nerve involvement and a single case of myelopathy (vision loss, sensorineural hearing loss, paraparesis, etc.) No mortalities were recorded.

Discussion
The diagnosis of neurobrucellosis is a challenging issue for both physicians and neurologists and requires a high index of suspicion especially in endemic areas as it can mimic other neurological disorders like viral meningoencephalitis, TB meningitis, cerebrovascular accidents, space occupying lesions, degenerative disk prolapse, multiple sclerosis, etc. Although a definitive diagnosis is possible only with culture, this was not applied here as the yielding results of the culture is low and delayed. In other words; the brucella organism is difficult to isolate in blood and CSF cultures (11,12). A rare but a definite risk of disease transmission to laboratory personnel (13,14)) was another reason for discarding it.

The diagnosis in our series was based on: a history of possible exposure, compatible clinical features, positive serology in blood and CSF (15,16,17), other abnormal CSF findings, CNS imaging(18,19), resolution of symptoms with
appropriate treatment\(^{(20,21)}\) and exclusion of other clinically similar neurological diseases in this setting.

Neurobrucellosis may involve several areas of the central and peripheral nervous systems and may develop at any stage of the disease\(^{(4,9,10,11,22)}\). In our series 4 major types of neurobrucellosis: meningitis and meningoencephalitis, cranial nerve palsy, radiculopathy and a single case of spastic paraplegia were recorded. Worldwide rare cases of other types like vascular (infarcts and haemorrhage), mycotic aneurysm, epidural and spinal cord abscesses\(^{(23,3)}\), Guillain Barre’s syndrome\(^{(24)}\), carpal tunnel syndrome\(^{(25)}\) etc. were all recorded.

Meningitis or meningo-encephalitis, are a well-known and a common type of neurobrucellosis during acute illness and can occur either as the only sign of infection or in the context of a systemic disease\(^{(26)}\), but it could occur in the setting of subacute and chronic infection\(^{(27,28)}\). The acute meningitis and meningoencephalitis are usually responding well to treatment if started early\(^{(29)}\).

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\(^{(30)}\).

There are few reports concerning cranial nerves involvement\(^{(31)}\), which may occur during acute and chronic infection, it may be the sole presenting feature of neurobrucellosis as in our cases or accompanies a brucella basal meningitis. Spastic paraplegia is a very rare neurological association with brucellosis\(^{(32,33)}\) but should be considered in the presence of strong clinical and serological evidence of brucellosis in blood and CSF in absence of well-known causes like multiple sclerosis, spinal abscesses, vertebral diseases, space occupying lesion...etc.

Positive serology and/or culture in CSF examination is an essential criterion for specific diagnosis in cases of CNS involvement but it is usually negative in pure cases of radiculo or peripheral neuropathy.

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 immunemediated process, or a vascular insult\(^{(18,19,34)}\). The major advantage of CNS scanning is in exclusion of some important neurological diseases like space occupying lesions (SOL). As brucella species are intracellular pathogens\(^{(1)}\), the treatment of neurobrucellosis may be an obvious challenge for physician even with combination antimicrobial therapy. Neurobrucellosis may be fatal if untreated but in most instances it responds to treatment especially if started early.

Despite the emergence of new antibiotics and different therapeutic approaches\(^{(20,21,29,35)}\), but still the World Health Organization (WHO) guidelines which recommend rifampin (600–900 mg) and doxycycline (200 mg) daily for a minimum of 6 weeks is applicable for treatment of neurobrucellosis in endemic areas\(^{(36)}\). We preferred to use such oral combination because they have good intracellular and CNS penetration and possible synergistic action in doses mentioned above which are relatively higher than doses used for uncomplicated brucellosis. Although blood and CSF serology and biochemistry are parts of follow up protocol in patients with neurobrucellosis, however the effectiveness and patient’s response to therapy in our patients was judged mainly on clinical basis. There is a controversy regarding the duration of therapy and some still using short course treatment for neurobrucellosis\(^{(29)}\) but the majority disagree with this because of serious nature of neurobrucellosis in addition to problem of relapses especially if treatment is
short\(^{(29)}\). The treatment course in our patients extended for at least 3 – 6 months.

A triple therapy by adding ceftriaxone\(^{(37,38)}\), since its high concentration in the cerebrospinal fluid which may offer significant efficacy against the pathogens was used only for two patients whose clinical response to initial two drugs was slow. Although 5-aminoglycosides (streptomycin and gentamicin) are used for treatment of uncomplicated brucellosis and even for neurobrucellosis\(^{(38)}\) but we discouraged their uses in our patients owing to their questionable ability to penetrate into the cerebrospinal fluid and their potential neurotoxicity that may perplex the clinical presentation\(^{(39)}\).

**Recommendations:**

1. Brucellosis is a preventable disease, and in those areas where it remains endemic like Iraq, authorities should initiate an active program to eliminate the disease by dealing with the animal reservoir and by pasteurization of milk and milk products.
2. As neurobrucellosis is fatal disease if not detect and treated early a prompt treatment of suspected cases is of crucial importance.

**References**

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الخلاصة:
داء البر وسيلة العصبي من الاختلاطات النادرة الحدوث لمرض البر وسيلة. هذه الدراسة تصف ستة عشر حالة من المرضى اعلاه ادخلوا مستشفيات (ابن سينا التعليمي، السلام ومستشفى الزهراوي الأهلي) الموصل للعلاج. اعتمد التشخيص على الاعراض والعلامات السريرية لدى المرضى وإيجابية الفحص المصلي، إضافة إلى فحص سائل النخاع الشوكي واستخدام جهاز الرنين المغناطيسي او المغشوض الطبقي للدماغ أو العضود الفقري. الصعاب، الحمى، التعزز، الخمول، الشعر بالتعب، تصلب الرقبة، اصابة الاعصاب القحفية، النعاس والام ظهر كانت من الاعراض الشائعة لدى المرضى. جميع المرضى تسلموا مجموعة متولدة من المضادات الحياتية لفترة 3 - 6 أشهر. ثمانية من المرضى تم شفاؤهم بالكامل أما الثمانية الاخرون فتركوا مع بعض العيوب البدنية أو الكلية. بما أن مرض البر وسيلة العصبي هو من الامراض القائمة إذا لم يتم معالجتها بحكرا فإنا يستعرضي أتباه أطباء العاملين في المناطق الموبوءة بالممرض كالمراقب الجماعي الانجابية بالمرض يعانون من أعراض عصبية أو نفسية غير مفروضة.