Journal of NeuroVirology, 16: 48–55, 2010

ISSN 1355-0284 print / 1538-2443 online
DOI: 10.3109/13550280903586386

informa
healthcare

Neuropsychiatric evaluation of patients with brucellosis

Ghaydaa A. Shehata,[1] Laila Abdel-Baky,[2] Heba Rashed,[3] and Hussein Elamin[4]

[1]Department of Neurology and Psychiatry; [2]Department of Tropical and Fever Diseases; [3]Department of Clinical Pathology; and [4]Department of General Medicine, Assiut University Hospital, Assiut, Egypt

Brucellosis is a multisystem disease that may present with a broad spectrum of clinical manifestations. Neurobrucellosis is one of the complications. The objective of this study was to determine neuropsychiatric manifestations among patients with brucellosis. Twenty-seven consecutive patients with brucellosis (14 patients with manifest neurological manifestation and 13 patients without apparent neurological manifestation) were recruited from Assiut University hospital and compared with 50 healthy controls matched with respect to age, sex, and social economic and educational levels. They were subjected to systemic, meticulous neuropsychiatric evaluations, laboratory, radiological, neurophysiology, and psychometric assessment with Mini-Mental State Examination, Wechsler Memory Scale–Revised. and Hamilton Depression Rating. Overt or apparent neurological manifestation was recorded in 14 patients (51.85%) and 13 patients (48.15%) with brucellosis without apparent neuropsychiatric involvement. Central nervous system (CNS) involvement (vascular stroke, meningeoencephalitis, and dementia) was recorded in 9 patients (33.3%) and 6 patients (22.2%) had peripheral nervous sytem (PNS) involvement (polyneuropathy, radiculoapathy, and polyradiculoneuropathy). Depression was recorded in 7 (29.2%) patients; 3 patients (21.4%) of the neurobrucellosis group and 4 patients (30.8%) with brucellosis without neurological manifestations. Patients with brucellosis (neurobrucellosis and patients without neurological manifestations) reported highly significant impairment in some cognitive function measures (mental control, logical memory, visual reproduction) and higher scores on depressive symptoms compared with controls. Patients with a *Brucella* infection usually manifest central nervous system involvement. Clinicians, especially serving in endemic areas or serving patients coming from endemic areas, should consider the likelihood of neurobrucellosis in patients with unexplained neurological and psychiatric symptoms, and should perform the necessary tests, including cognitive function and depression tests. *Journal of NeuroVirology* (2010) **16,** 48–55.

Keywords: brucellosis; cognitive function; depression; neurobrucellosis

Introduction

Brucellosis is the most common zoonotic infection in the world. It infects animals as the primary host (e.g., camels, sheep, and goats) and humans as the secondary host (Al-Kawi *et al*, 1995; Al Deeb *et al*, 1988). The organisms are gram-negative short rods that are usually transmitted in the consumption of uncooked meat or unpasteurized dairy products (Al-Kawi *et al*, 1995; Al Deeb *et al*, 1988; Shakir, 1996). More than 500,000 new cases occur annually, but with an uneven global distribution (Skalsky *et al*, 2008). Areas currently listed as high risk are the Mediterranean Basin (Portugal, Spain, Southern France, Italy, Greece, Turkey, and North Africa), South and Central America, Eastern Europe, Asia, Africa, the Caribbean, and the Middle East (Gul *et al*, 2009). Seroprevalence for *Brucella* antibodies is 1%

Address correspondence to Dr. Ghaydaa Ahmed Shehata, MD, Lecturer of Neurology, Department of Neurology and Psychiatry, Assiut Univeristy Hospital, Assiut, 7111 Egypt. E-mail: ghaydaa83@yahoo.com
Received 3 September 2009; revised 22 November 2009; accepted 12 December 2009.

to 7% in Turkey and Iraq, and 10% in Egypt. More than 40% of all cases of fever of unknown origin in Egypt are believed to be due to brucellosis (Rust, 2004).

Neurobrucellosis is uncommon and neurological manifestations of neurobrucellosis are diverse, and can affect any part of the central or peripheral nervous system. Also, the clinical picture may be confused by the coexistence of two or more clinical syndromes in the same patient (Al Deeb *et al*, 1988). However, neurobrucellosis may develop at any stage of disease and may have widely variable manifestations, including encephalitis, meningoencephalitis, radiculitis, myelitis, peripheral and cranial neuropathies, subarachnoid hemorrhage, and psychiatric manifestations (Eren *et al*, 2006). The psychiatric manifestations in neurobrucellosis reported before were depression, amnesia, psychosis, agitation, nightmares, personality disorder, and euphoria, in case reports or case series (Shakir *et al*, 1987). Central nervous system involvement occurs in 5% to 7% of all cases, but evidence of the nervous system dysfunction (peripheral and central) are reported in 5% to 10% of chronic brucellosis (Ghaffarpour *et al*, 2007).

Interleukin-6 (IL-6) is an interleukin that acts as both a proinflammatory and anti-inflammatory cytokine. It is secreted by T cells and macrophages to stimulate immune response to trauma, infections, or other tissue damage leading to inflammation (van der Poll *et al*, 1997; Le Moine *et al*, 1994).

This study was designed to determine neuropsychiatric manifestations among patients with brucellosis and to determine the relation between interleukin-6 (IL-6) and neuropsychiatric involvement in neurobrucellosis.

Results

Demographic and clinical data and laboratory findings of patients were given in Table 1. There were nonsignificant differences between any groups of the patients with brucellosis, and control group or between two groups of brucellosis in demographic data. Fever was the most common (100%) symptom, followed by hepatospleenomegaly (63%). Manifest neurological symptoms and signs (neurobrucellosis group) were recorded in 14 patients (51.85%) and 13 patients (48.15%) with brucellosis without apparent neurological symptoms and signs. Using paired-sample *t* test, there was significant decline of ESR level in patient group, from 118.7 ± 34.7 mm/h (at admission, i.e., before beginning of treatment in patient group) to

Table 1 Epidemiologic, clinical, and laboratory findings of studied groups

		Patients (N = 27)			P values	
	Control (N = 50)	Total patients (N = 27)	Neurobrucellosis cases (N = 14)	Brucellosis cases without neurological involvement (N = 13)	*P1*	*P2*
Age	44.14 ± 7.10	41.07 ± 15.66	42.21 ± 16.94	39.85 ± 14.74	.575	.073
Gender (M/F)	29/21	16/11	8/6	8/5	.968	
Living in rural area	39 78 %	22 81.5%	12 85.7%	10 76.9%	.800	
Number of educated years	4.38 (0–9)	3.44 (0–9)	4.2 (0–9)	3.5 (0–9)	.981	.284
Socioeconomic state score	12.42 ± 2.83	11.63 ± 2.98	11.71 ± 3.31	11.54 ± 2.69	.875	.254
Symptoms						
Fever	— —	27 (100%)	14 (100%)	13 (100%)	— .038*	
Sweating	— —	15 (55.6%)	5 (35.7%)	10 (76.9%)	.573 .000*	
Arthralgia		14 (51.9%)	7 (50.0%)	7 (53.8%)		
Hepato-splenomegaly		17 (63.0%)	14 (100.0%)	3 (23.1%)		
Laboratory findings						
ALT (U/L)	12.0 ± 3.2	29.6 ± 4.6	28.6 ± 9.7	30.8 ± 11.2	.057	NS
AST (U/L)	12.0 ± 3.2	29.6 ± 4.6	29 ± 12.3	31 ± 7.9	.057	NS
ESR (mm/h)	9.0 ± 0	118.7 ± 34.7	113.93 ± 41.6	123.92 ± 76.4	.000	NS
IL-6 (pg/ml)	7.3 ± 0.7	267.63 ± 14.66	301.4 ± 56	231.23 ± 37.4	.000	.034

Note. P1: comparison between total patients and control; *P2*: comparison between neurobrucellosis and patients with brucellosis without neurological symptoms. ALT; alkaline transaminase (normal value = 0–35 U/L); AST (SGOT): 0–35 U/L; ESR: erythrocyte sedimentation rate (normal when less than 10 mm/h); IL6: interleukin-6 (normal value = 3–8.5 pg/ml); NS: nonsignificant, and the mean difference is significant at the .05 level.

11.1 ± 4. 3 mm/h (after treatment); P =.000. There was also significant decline of IL-6, from 267.63 ± 14.6 pg/ml (at admission, i.e., before beginning of treatment in patient group) to 9.26 ± 4.1 pg/ml (after treatment); P =.000.

Central nervous system (CNS) involvement was recorded in nine patients (33.3%); three had ischemic stroke, two of them had cerebellar infarction (one was apparent and the other was detected clinically by soft neurological signs impairment) documented by magnetic resonance imaging (MRI), and one had bilateral pyramidal and cerebellar affection in which MRI finding was multiple infarction. One patient developed dementia documented by Mini-Mental State Examination (MMSE) in which his score was 13/30. Five patients had meningeoencephalities, and MRI and electroecncephalography (EEG) were performed on them. Six patients (22.2%) had peripheral nervous system (PNS) involvement. The clinical signs, symptoms, nerve conduction studies with F-waves, and MRI of lumbosacral regions of two patients (7.4%) were compatible with polyradiculoneuropathy. Peripheral neuropathy of mixed sensory and/or motor type were also observed in three patients (11.1%). Radiculopathy was observed in one patient (3.7%). And one had combined central and peripheral nervous systems affection. All patients with brucellosis were interviewed, and the diagnosis of mild depression due to a general medical condition was recorded in seven patients (29.2%), as showed in Table 2.

The mean score of MMSE among neurobrucellosis patients was significant lower than the control group (P =.004). In addition, it was significantly lower than patients with brucellosis without neurological involvement (P =.012).

Neuropsychiatric scales showed no significant differences in digit forward and associate learning between brucellosis patients and controls. However, mental control, logical memory, visual reproduction, and Hamilton Depression Rating Scale (HDRS) score were significantly lowered in both groups compared with the control group. There were significant decline in digit backward, mental control, and total Wechsler Memory Scale (WMS) score in the neurobrucellosis group compared with patients with brucellosis without manifest neurological involvement (Table 3). No significant correlation was found between duration of illness, laboratory findings, or clinical symptoms with cognitive function and depression scales.

To examine the relation between IL-6 and neuropsychiatric involvement in patients with brucellosis, a series of Pearson correlation coefficients were calculated. Significant positive correlation was found between IL-6 and Hamilton Depression Scale score, whereas significant negative correlation was found between IL-6 and some studied cognitive function as in Table 4.

Discussion

The spectrum of nervous system manifestations of patients with brucellosis is very broad and has been found to include subtle subclinical neurological and cognitive dysfunctions that may be detected only by meticulous examination and neuropsychological evaluation. This is true in the present study, in which 5 (38.5%) out of 13 patients with brucellosis without manifest neurological symptoms had depression or cerebellar affection, in addition to significant impairments in some cognitive function, as mental control, logical memory, and visual reproduction were detected in that group in comparison with control group. In the present study, the manifest neurobrucellosis was reported in 51.85% and subtle neuropsychiatric affection of patients without manifest neurological affection, who are diagnosed only by meticulous neurological assessment and applied psychometric scales. In previous studies, neurobrucellosis was reported in a wide range of proportions (0% to 25%) among patients with brucellosis (Shakir *et al*, 1987; Lubani *et al*, 1989; Sanchez-Sousa *et al*, 1990). This large variation is attributable to the lack of standardization of diagnostic criteria used by different authors. In this study, the assessment made use of soft neurological signs, MMSE, WMS, and HDRS tests, in which subtle or occult neuropsychiatric signs were detected among patients with brucellosis. Several hypotheses have been suggested to explain the wide spectrum of neuropsychiatric manifestations of brucellosis. 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 immunological and inflammatory reactions of the host to the presence of these organisms within the nervous system or within other tissues of the body. The importance of inflammatory mediation of some forms of tissue injury during the acute stage of brucellosis is suggested by the occurrence, in some patients, of brain edema (Shakir *et al*, 1987; Sanchez-Sousa *et al*, 1990). While in chronic state, neurobrucellosis might be due to persistent intracellular effects of the organism, or perhaps the infection might trigger an immune mechanism leading to demyelination (Abramsky, 1977). Interleukin-6 plasma level was considered as the most sensitive and specific tool for the diagnosis of bacterial infection (Le Moine *et al*, 1994). In this study, there were significant increase in level of IL-6 among patients with neurobrucellosis compared to patients with brucellosis without manifest neurological signs and highly significant decline in its level after treatment. These results matched those of a previous study (Krishnan *et al*, 2005) in which the authors examined the expression of multiple cytokines in the cerebrospinal fluid (CSF) of a patient with neurobrucellosis using cytokine antibody arrays and found a marked elevation of interleukin

Table 2 Neuropsychiatric, radiological, and neurophysiological data of patients with brucellosis

Patient number/age (years)/sex	Classify group	CNS	PNS	Depression	MRI	Neurophysiology
1/64/F	1	—	Polyradiculoneuropathy	Depressed	Not performed	Polyradiculoneuropathy
2/63/F	1	Meningeoencephalities + demented	—	Depressed	Diffuse hyperintence lesions	
3/61/M	1	CNS Clinically free	Polyneuropathy	Depressed	Not performed	Polyneuropathy
4/18/M	1	CNS Clinically free	Polyradiculopathy	Not depressed	Not performed	Polyradiculopathy
5/27/F	1	CNS Clinically free	Polyradiculoneuropathy	Not depressed	Not performed	Polyradiculoneuropathy
6/50/F	1	CNS Clinically free	Polneuropathy	Not depressed	Not performed	Polyneuropathy
7/18/F	1	CNS Clinically free	Polneuropathy	Not depressed	Not performed	Polyneuropathy
8/54/M	1	Meningeoencephalities	PNS Clinically free	Not depressed	Diffuse hyperintence lesions	Not performed
9/42/M	1	Meningeoencephalities	PNS Clinically free	Not depressed	Diffuse hyperintence lesions	Not performed
10/45/M	1	Meningeoencephalities	PNS Clinically free	Not depressed	Diffuse hyperintence lesions	Not performed
11/30/F	1	Encephalitis	PNS Clinically free	Not depressed	Diffuse hyperintense lesions	Not performed
12/45/M	1	Cerebrovascular stroke	Sensory polyneuropathy	Not depressed	Multiple hyperintense lesions	Not performed
13/19/M	1	Cerebrovascular stroke	PNS Clinically free	Not depressed	Cerebellar hyperintense lesions	Not performed
14/55/M	1	Cerebrovascular stroke	PNS Clinically free	Not depressed	Cerebellar hyperintense lesions	Not performed
15/35/M	2	Clinically free	PNS Clinically free	Depressed	Not performed	Not performed
16/26/F	2	Clinically free	PNS Clinically free	Depressed	Not performed	Not performed
17/30/M	2	Clinically free	PNS Clinically free	Depressed	Not performed	Not performed
18/19/M	2	Clinically free	PNS Clinically free	Depressed	Not performed	Not performed
19/47/M	2	Positive soft signs of coordination	PNS Clinically free	Not depressed	Cerebellar hyperintense lesions	Not performed
20/55/F	2	Clinically free	PNS Clinically free	Not depressed	Not performed	Not performed
21/45/M	2	Clinically free	PNS Clinically free	Not depressed	Not performed	Not performed
22/55/F	2	Clinically free	PNS Clinically free	Not depressed	Not performed	Not performed
23/55/F	2	Clinically free	PNS Clinically free	Not depressed	Not performed	Not performed
24/45/M	2	Clinically free	PNS Clinically free	Not depressed	Not performed	Not performed
25/37/F	2	Clinically free	PNS Clinically free	Not depressed	Not performed	Not performed
26/50/M	2	Clinically free	PNS Clinically free	Not depressed	Not performed	Not performed
27/19/M	2	Clinically free	PNS Clinically free	Not depressed	Not performed	Not performed

Note. Group 1: patients with neurobrucellosis; group 2: patients with brucellosis without manifest neurological involvement. M: male; F: female.

Table 3 Neuropsychiatric scores among studied groups

Variables	Control (N =50)	Neurobrucellosis (N = 14)	Patients with brucellosis without manifest neurological symptoms (N = 13)	*P1*	*P2*	*P3*
Total MMSE	28.32 ± 2.01	26.07 ± 4.28	28.45 ± 1.60	.004	.781	.012
Digit forward	5.56 ± 0.76	5.61 ± 0.89	5.84 ± 0.95	.825	.280	.483
Digit backward	3.38 ± 1.01	1.82 ± 0.46	3.23 ± 1.98	.000	.713	.006
Mental control	3.98 ± 0.14	2.28 ± 1.17	3.23 ± 1.98	.000	.001	.000
Logical memory	12.44 ± 1.87	8.31 ± 2.82	9.27 ± 2.50	.000	.000	.254
Associate learning	10.62 ± 2.95	11.51 ± 3.97	12.81 ± 4.54	.394	.45	.332
Visual reproduction	4.08 ± 1.55	2.10 ± 1.36	2.92 ± 0.90	.000	.011	.143
Total WMS	39.74 ± 4.98	31.41 ± 9.12	37.12 ± 8.29	.000	.201	.025
HDRS	0.16 (0–2)	7.25 (0–35)	8.58 (0–35)	.000	.000	.527

Note. MMSE: Mini-Mental State Scale; WMS: Wechsler Memory Scale; HDRS: Hamilton Depression Rating Scale. *P1*: comparison between control group and patients with neurobrucellosis. *P2*: comparison between control group and patients with brucellosis without manifest neurological symptoms. *P3*: comparison between neurobrucellosis and patients with brucellosis (without manifest neurological symptoms).

Table 4 Correlation between IL-6 and cognitive function and depression

Variables	r	P
Attention	$-.267^a$	.019
Recall	$-.221^a$	.053
Digit backward	$-.299^b$	.008
Mental control	$-.664^b$	.000
Logical memory	$-.497^b$	.000
Visual memory	$-.430^b$	.000
Total WMS	$-.341^b$	.002
HDRS	$.378^b$	.001

(IL-6) and its level returned to baseline following treatment of the patient. That could be explained by the theory that suggested that neurobrucellosis occurred due to inflammatory mechanism (Shakir *et al*, 1987; Sanchez-Sousa *et al*, 1990; Abramsky, 1977). In addition, there were significant correlation between IL-6 and cognitive impairment and positive correlation with depression.

Gul *et al* (2009) reported that cerebrovascular disease involvement in neurobrucellosis is explained mainly by two mechanisms. The first mechanism is rupture of a mycotic aneurysm. The other mechanism is the inflammatory process of the vessels, particularly arteritis, with resultant lacunar infarcts, small hemorrhages, venous thromboses, or vasculitis.

Clinical features of myeloradiculopathy have been widely described. This condition can result from infectious arachnoiditis of the spinal cord or infectious vasculitis, leading to medullary infarcts. Distinction from compressive myelopathy by extradural abscess or granuloma secondary to brucellar spondylitis must be established by myelography Nimri (2003). In this study, the high incidence of CNS and PNS involvement, together with cognitive function and psychiatric affection, suggests that a single pathogenic mechanism is not likely to be valid for every neuropsychiatric manifestation occurring in patients with brucellosis.

The psychiatric manifestations reported before were depression, amnesia, psychosis, agitation, nightmares, personality disorders, and euphoria (Shalsky *et al*, 2008; Gul *et al*, 2009; Eren *et al*, 2006; Bucher *et al*, 1990; Pascual *et al*, 1988). In this study, depression was detected in seven patients (29.2%); three of them have manifest neurobrucellosis, whereas four were apparently without any neuropsychiatric involvement. Depression is significantly more present in patients with brucellosis without manifest neurological symptoms than in patients with manifest neurological symptoms. The explanation of that could be explained by the mechanism of depression in these patients with brucellosis does not depend only upon depression due to neurological illness, but it also points to different mechanisms such as direct effect of the organism or its products on the meninges and brain (Akdeniz *et al*, 1998). The psychiatric changes in neurobrucellosis were reported previously, but were not described based on objective criteria. In this study, we used MMSE, WMS, and HDRS tests as the most suitable tools. In addition, there are impaired cognitive functions, primarily mental control, logical memory, visual memory and reproduction among neurobrucellosis cases and also among patients without neurological manifestations. In addition, patients with neurobrucellosis are reported to have more decline in cognitive function, disturbances of orientation, memory, and attention, and poverty of content are seen without unconsciousness and without deterioration of general status.

Conclusion

In patients with brucellosis, neuropsychiatric abnormality is fairly common in patients with apparent neurological involvement (neurobrucellosis) and those without. The cognitive and emotional disturbances could be seen among neurobrucellosis patients. The use of such tests favors a true incidence

of nervous system involvement, more accurate diagnosis, and better clinical care before the development of debilitating CNS and PNS changes.

Patients and study

Assiut University Hospital is the largest referral and tertiary-care community hospital in Upper Egypt. This study was a prospective descriptive cross-sectional study performed in the Departments of Tropical and Fever Diseases and Neurology, in collaboration with the Departments of Clinical Pathology and General Medicine of the hospital, between October 2006 and October 2008. Demographic data, history, physical examination, laboratory results, test scores, antibiotic treatment, and follow-ups were recorded on individual forms.

Twenty-seven consecutive patients with brucellosis (14 patients with manifest neurological manifestation and 13 patients without apparent neurological manifestation) were recruited from 100 patients with fever of unknown etiology, represented 27% of them. The diagnosis of brucellosis was based on compatible clinical findings and a serum agglutinin titer of 1/160 in standard tube agglutination test (STA) or a positive blood culture. Neurobrucellosis was diagnosed by the following criteria: (i) symptoms or clinical findings compatible with neurobrucellosis; (ii) isolation of *Brucella* spp. from cerebrospinal fluid (CSF) and/or demonstration of antibodies to *Brucella* with titre of 1/4 in the CSF; (iii) the presence of the following findings: lymphocytosis, increased protein, and decreased glucose levels in the CSF; and (iv) clinical improvement with appropriate treatment. Magnetic resonance imaging (MRI), electroencephalography (EEG), electromyography with nerve conduction velocity (EMG + NCV), and abdominal sonar investigations were performed according to need. Antibiotic treatment (according to the Department of Tropical and Fever Diseases, Assiut University Hospital, protocol) for brucellosis was given to all the patients for 6 weeks and different combinations of ceftriaxone (2 g intravenously [i.v.], twice daily [b.i.d.]), rifampicin (600 mg/day orally [p.o.]), and doxycyclin (100 mg p.o., b.i.d.) were given. Full clinical data and laboratory investigations were done, which included measurment of interleukin-6 by enzyme-linked immunosorbent assay (ELISA), sandwich technique (Le Moine *et al*, 1994). Liver function tests by spectrophotometeric method using stat fax (Bock, 2003) and erythrocyte sedimentation rate (ESR) using Western green tubes method (Van den Borck and Letsky, 2002).

ESR, liver functions, and IL-6 tests were done at time of admission (before the beginning of treatment) and at discharge of patients (within 2 weeks from admission), to assess the response to treatment in order to documented the diagnosis.

The patients were compared with 50 healthy controls matched with respect to age, sex, educational level, and socioeconomic status (Fahmy and El-Sherbini, 1983). The regional ethical committee of Assuit University Hospital approved this study. All subjects (themselves or their caregivers) gave their informed consent for participation.

Assessment procedures

Demographic and clinical characteristics

Baseline medical, neurological, and psychiatric assessments were done within 1 week of admission (the neuropsychological assessments were performed blinded and before the classification of patient's status: with or without neurological involvement). Demographic data, including age, sex, educational level, occupation, and socioeconomic status (Fahmy and El-Sherbini, 1983), and duration of illness were collected.

Soft neurological sign assessment

Patients with brucellosis without neurological manifestation had a structured neurological soft sign examination at baseline, as described by Hollander *et al* (1990). This was found to have very good interrater reliability, which ranges from 0.58 to 0.95 (Hollander *et al*, 1990). The neurological soft sign examination is divided into four categories: coordination, involuntary movements, sensory, and visuospatial function. Coordination was assessed for accuracy in the following areas: finger to finger, finger to nose, heel to shin, finger to thumb, rapid alternating movements, mirror movements, hopping, and toe and heel walking. Involuntary movement testing included standing in the Romberg position, with the first 20 s assessing station and motor persistence. For the next 20 s, assessment of athetosis, chorea, tremor (resting and intention), and abnormal posturing was conducted. Sensory function included testing for astereognosis, agraphesthesia, position sense, and direction of cutaneous kinesthesia. Visuospatial station was assessed using the face-hand test, right-left confusion on self and examiner, and cube drawing. In testing right-left confusion, right and left side body parts on the patient and examiner were tested for misidentification.

Cognitive and depression assessment

A detailed neuropsychological assessment was done for all patients (except two patients who were comatose) and controls, within 1 week of admission. A set of standardized neuropsychological tests that are sensitive for mild cognitive impairment and covering different cognitive domains were selected. Each patient was tested on 2 separate days and on separate occasions in the same day to complete the total battery of testing and avoid exhaustion of patients. The primary outcome variables were scored by the use of the following instruments: (1) Mini-Mental State Examination (MMSE) (Folstein *et al*, 1975), a widely used scale for the screening test for dementia.

It has a maximum score of 30 points. As most of the subjects of the present study were illiterate or with low education levels, we excluded the two points testing reading and writing, and the full score was calculated as 28 instead of 30 points. The lower value for regarding a subject as dementia suspect was 21 instead of 23 points (Farrage *et al*, 1998). MMSE takes 5 to 10 min to administer. (2) Wechsler Memory Scale–Revised (WMS-R) (Weshler, 1987) is useful for mild memory impairment, where sensitivity is needed. Selected tests included digit forward, digit backward, mental control, associate learning, logical memory, and visual reproduction. It takes 25 to 30 min to administer. (3) The Hamilton Depression Rating Scale (HDRS) (Hamilton Depression Scale, 1976; Hamilton, 1960) is a 17-item scale that evaluates depressed mood, vegetative and cognitive symptoms of depression, and comorbid anxiety symptoms. It provides ratings on current *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), symptoms of depression, with the exceptions of hypersomnia, increased appetite, and concentration/indecision. The maximum score was 53 for the entire test. Scores between 0 and 7 mean there is no depression, between 8 and 27 mean mild depression, between 28 and 41 mean moderate depression, and between 42 and 53 mean severe depression (Eren *et al*, 2006).

Statistical analysis

Data obtained from this study were input into an IBM compatible computer. Descriptive statistics, i.e., mean, standard deviation, and percentages were calculated using a computer software package (SPSS for windows, version 16). Statistically comparison using independent samples *t* test, paired *t* test (to compare between ESR and IL-6 before beginning of treatment and after 2 weeks from starting the treatment), and one-way analysis of variance (ANOVA) followed by least significant difference (LSD) *post hoc* test were applied to compare mean values of the studied groups. Pearson correlation coefficient was applied to study the relation between IL-6 and neuropsychiatric affection.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

Abramsky O (1977). Neurological features as presenting manifestations of brucellosis. *Eur Neurol* **15:** 281–284.

Akdeniz H, Irmak H, Anlar O, Demiroz AP (1998). Central nervous system brucellosis: presentation, diagnosis and treatment. *J Infect* **36:** 297–301.

Al Deeb S, Yaqub B, Sharif H, Al-Rajeh SM (1988). Neurobrucellosis. In: *Hereditary neuropathies and spinocerebellar atrophies*, revised series 16. Vinken PJ, Bruyn GW, Klawans HL (eds). Amsterdam: Elsevier Science Publishers; pp 581–601

Al-Kawi MZ (1995). Brucellosis. In: *Guide to clinical neurology*. Moher JP, Gautier J (eds). New York: Churchill Livingstone, pp. 677–680

Bock BJ (2003). The data warehouseas a foundation for population-based reference intervals. *Am J Clin Pathol* **120:** 262–70.

Bucher A, Gaustad P, Pape E (1990). Chronic neurobrucellosis due to Brucella melitensis. *Scand J Infect Dis* **22:** 223–226.

Eren S, Bayam GK, Ergönül O, Aelikbasx AC, Pazvantoğlu O, Baykam NA, Dokuzoğuz B, Dilbaz N (2006). Cognitive and emotional changes in neurobrucellosis *J Infect* **53:** 184–189

Fahmy SI, El-Sherbini AF (1983). Determining simple parameters for social classification for health research. *Bull High Inst Public Health* **8:** 95–108.

Farrage AF, Farweez HM, Kheder EH, Mahfouz RM, Omran MS (1998). Prevalence of AD and other dementing disorders: Assuit–Upper Egypt Study. *Dement Geriatr Cogn Disord* **9:** 323–328.

Folstein MF, Folstein SE, McHugh PH (1975). "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* **12:** 189–198.

Ghaffarpour M, Khoshroo1 A, Harirchian MH, Sikaroodi H, Pourmahmoodian H, Jafari S, Hejazi SS (2007). Clinical, epidemiological, laboratory and imaging aspects of brucellosis with and without neurological involvement. *Acta Med Iran* **45:** 63-68.

Gul HC, Erdem H, Bek S (2009). Overview of neurobrucellosis: a pooled analysis of 187 cases. *Int J Infect Dis* **13:** e339–43.

Hamilton Depression Scale (1976). In: *ECDEU Assessment Manual*. US Department of Health and Human Services, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, pp 180–192.

Hamilton M (1960). Rating scale for depression. *J Neurol Neurosurg Psychiatry* **53:** 56-62.

Hollander E, Schiffman E, Cohen B, Rivera-Stein MA, Rosen W, Gorman JM, Fyer AJ, Papp L, Liebowitz MR (1990). Signs of central nervous system dysfunction in obsessive-compulsive disorder. *Arch Gen Psychiatry* **47:** 27–32.

Klawans HL (eds). Amsterdam: Elsevier Science Publishers; pp 581–601.

Krishnan C, Kaplin AI, Graber JS, Darman JS, Kerr DA (2005). Recurrent transverse myelitis following neurobrucellosis: immunologic features and beneficial response to immunosuppression. *J NeuroVirol* **11:** 225–231.

Le Moine O, Devière J, Devaster JM, Crusiaux A, Durand F, Bernuau J, Goldman M, Benhamou JP (1994). Interleukin-6: an early marker of bacterial infection in decompensated cirrhosis. *J Hepatol* **20:** 819–824.

Lubani MM, Dudin KI, Araj GF, Manandhar DS, Rashid FY (1989). Neurobrucellosis in children. *Pediatr Infect Dis J* **8:** 79–82.

Nimri LF (2003). Diagnosis of recent and relapsed cases of human brucellosis by PCR assay. *BMC Infect Dis* **28:** 3–5.

Pascual G, Combarros O, Polo JM, Berciano J (1988). Localized CNS brucellosis. *Acta Neurol Scand* **78:** 282-289.

Rust RS. (2004). Brucellosis available at CDC (Centers for Disease Control and Prevention). http://www.cdc.gov/ncidod/dbmd/diseaseinfo/. Accessed at June 2009.

Sanchez-Sousa A, Torres C, Campello MG, Garcia C, Parras F, Cercenado E, *et al* (1990). Serological diagnosis of neurobrucellosis. *Clin Pathol* **43:** 79–81.

Shakir RA, Al-Din AS, Araj GF, Lulu AR, Saadah MA (1987). Clinical categories of neurobrucellosis: a report on 19 cases. *Brain* **110:** 213–223.

Shakir RA. Brucellosis. In: Shakir RA, Neuman PK, Poser CM (eds) (1996). *Tropical neurology*. Cambridge: WB Saunders, pp 168–179.

Skalsky K, Yahav D, Bishara J, Pitlik S, Leibovici L, Paul M (2008). Treatment of human brucellosis: systematic review and Meta analysis of randomized controlled trials. *BMJ* **336:** 701–704.

Van den Borck NR, Letsky EA (2002). Pregnancy and erythrocyte sedimentation rate. *Br J Obstet Gynecol* **108:** 1164–1167.

van der Poll T, Keogh CV, Guirao X, Buurman WA, Kopf M, Lowry SF (1997). Interleukin-6 gene-deficient mice show impaired defense against pneumococcal pneumonia. *J Infect Dis* **176:** 439–444.

Wechsler D (1987). *Wechsler Memory Scales–Revised*. New York: Psychological Corporation.

This paper was first published online on Early Online on 13 February 2010.