Different manifestations of nervous system involvement by neurobrucellosis

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ABSTRACT

الأهداف: تقييم الفئات السريرية والمخبرية ونتائج الأشعة ونتائج المعالجة للمرضى المصابين بالبروسليات العصبية.

الطريقة: أجريت هذه الدراسة الوصفية بقسم الأمراض المعدية والميكروبات السريرية بكلية الطب بجامعة غازينتيب – تركيا، في الفترة ما بين عام 2003م وحتى 2006م. تم تشخيص حالة 300 مريض يعاني من البروسليات و13 مريض من البروسليات العصبية. كان تشخيص البروسليات العصبية مبنياً على عزل بكتريا البروسليات (spp)، من السائل النخاعي الشوكي (CSF) و/أو (تراص أنبوب STA القياسي 1/40≥)، لوحظ زيادة الخلايا اللمفاوية في السائل النخاعي الشوكي (CSF)، وزيادة البروتين في السائل النخاعي الشوكي (CSF) و(STA) أكبر من أو يساوي (1/320≥) في الدم. كانت مستويات ديمينيس ادينوسين (12.15u/L) في السائل النخاعي الشوكي (CSF)، تتفاوت فترة المعالجة بالمضادات الميكروبية مع الاستجابة السريرية للمريض.

النتائج: قمنا بتقسيم الثلاثة عشر مريضا المصابين بالبروسليات العصبية إلى أربعة مجموعات مختلفة سريرياً: التهاب السحايا والدماغ في 8 مرضى، زوال النخاعين في الدماغ لدى مريض واحد، والالتهاب النخاع الشوكي لدى مريض واحد، والاضطراب النفسي العصبي لدى ثلاثة مرضى. كان أكثر الأشكال السريرية شيوعاً من البروسليات العصبية هو التهاب السحايا والدماغ. لم يكن هنالك وفيات في أي من الحالات.

خاتمة: يمكن بتطبيق هذه الفئات التشخيصية المساعدة في التشخيص المبكر للبروسليات العصبية والتفريق بين الإصابات الأخرى للجهاز العصبي المركزي في المنطقة المستوطنة.

Objectives: To assess the clinical categories, laboratory, radiological findings, and treatment outcomes of patients with neurobrucellosis.

Methods: This retrospective study was designed at the Infectious Diseases and Clinical Microbiology Department, Faculty of Medicine of Gaziantep University, Gaziantep, Turkey between 2003 and 2006. In this period, 300 patients with brucellosis were diagnosed, and 13 patients with neurobrucellosis are described. Diagnosis of neurobrucellosis was based on the isolation of Brucella spp. from CSF and/or CSF standard tube agglutination (STA) ≥1/40, lymphocytic pleocytosis, increased protein in CSF and STA ≥1/320 in blood. The mean adenosine deaminase level was 12.15 u/L in CSF. The duration of antimicrobial treatment varied with the clinical response of the patient.

Results: We divided the 13 patients with neurobrucellosis into 4 different groups according to clinical presentation: meningoencephalitis in 8 patients, cerebral demyelination in one patient, myelitis in one patient, and neuropsychiatric disorder in 3 patients. The most common clinical form of neurobrucellosis was meningoencephalitis. There was no mortality in any of the cases.

Conclusion: Applying these diagnostic criteria can help both early diagnosis of neurobrucellosis and differentiation from other CNS involvement in endemic regions.

Neurosciences 2008; Vol. 13 (3): 283-287

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Received 20th October 2007. Accepted 29th March 2008.

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Brucellosis is a zoonotic infectious disease widespread in the Mediterranean zone, which also involves Turkey. Transmission occurs through direct contact with infected animals, it can also be acquired by indirect exposure, such as consuming unpasteurized milk and dairy products.[1] Brucellosis can affect all systems of the body, and so, its clinical syndromes are ultimately diverse. Central nervous system involvement is a rare manifestation of brucellosis.[1,2] Clinical presentation can comprise a broad spectrum ranging from meningitis

and meningoencephalitis to peripheral neuropathy, radiculopathy, cerebrovascular complications, depression, and psychiatric disorders.[3] Coexistence of 2 or more clinical syndromes in the same patient can lead to confusion and delay in diagnosis. We aimed to analyze the different clinical presentations of this endemic disease in the Southeastern part of Turkey. Thirteen patients with neurobrucellosis treated in our clinic were documented in this retrospective study. Clinical presentation, laboratory findings, diagnostic criteria, differentiation from other CNS involvement and also therapy were reported.

Methods. Our hospital is in the Southeastern Anatolia Region, which is a zone that brucellosis is seen endemically. This retrospective study was designed at the Infectious Diseases and Clinical Microbiology Department of Gaziantep University Faculty of Medicine between 2003 and 2006. In this period 300 patients with brucellosis were diagnosed, and 13 patients with neurobrucellosis are described. Patients included in this study fulfilled the criteria of brucellosis and neurobrucellosis defined as follows: The diagnosis of brucellosis was made based on at least one of the following criteria: Isolation of Brucella spp. in blood or other body fluids or in the tissue samples and/or clinical presentation with brucellosis in the presence of positive standard tube agglutination test (STA) ≥1/160, or at least a four-fold increase in this titer in a 2-3 week interval. The diagnostic criteria for neurobrucellosis were identified. These criteria were: (a) neurological involvement, which cannot be explained by other neurological pathology (b) isolation of Brucella spp. from CSF or positive STA ≥1/40 in CSF and abnormal CSF findings (lymphocytic pleocytosis, increased protein). Exclusion criteria included the diagnosis of other neurological diseases or any infectious disease due to other microorganisms. In all patients, age, gender, occupation, other diagnoses within the last 6 months, clinical symptoms, physical examination findings, neurological findings, blood and CSF brucella agglutination titers, CSF analyses (cell numbers, protein amount and glucose level), adenosine deaminase (ADA) levels in CSF, radiological findings and treatment results were analyzed. Blood, CSF, and other samples were cultured in the BacT-Alert (bioMerieux) automated system and were incubated for at least 21 days. Seroagglutination tests (STA, Brucella abortus, M101, Croma test, Linear Chemical, Spain) were performed by way of the STA. Treatment protocols were rifampicin, doxycycline, and ceftriaxone for 2 weeks, then continued to rifampicin, doxycycline, and trimethoprim sulfamethoxazole until the end of the therapy. The duration of antimicrobial treatment varied with the clinical response of the patient. In patients with prolonged clinical improvement and absence of complete normalization of CSF findings, the treatment was prolonged to 6-9 months. Treatment doses were given as rifampicin (600 mg/24h), doxycycline (100 mg/12h), ceftriaxone (2 g/12h) and trimethoprim-sulfamethoxazole (160-800 mg/12h). Prednisolone 40-60 mg/day was given orally to patients 8, 9, 10, and 11 for 4-6 weeks.

Results. Patients diagnosed with neurobrucellosis were classified into 4 different clinical pictures according to major clinical findings and onset time of clinical presentation. Clinical presentation and laboratory findings of patients are shown in **Tables 1 & 2**. Complaints, physical examination findings, some imaging findings, and treatment protocols are summarized in **Table 3**. The incidence of neurobrucellosis in all brucellosis was 4%, the mean age was 39.9±15.8 years; the female/male ratio was 9/4.

Table 1 - Clinical presentation of patients with neurobrucellosis.

Patient no	Age/ Gender	Brucellosis history/ duration	Duration of symptoms	Diagnosis at onset of symptoms	Diagnosis at psychiatry clinic
1	F/30	-	10 days	Encephalitis	-
2	M/46	-	15 days	Cervical lymphadenopathy	-
3	F/17	-	15 days	-	-
4	F/65	+/2 months	30 days	Tuberculous meningitis	-
5	M/67	+/3 months	27 days	-	-
6	F/56	+/6 months	15 days	-	-
7	F/43	+/3 months	22 days	-	-
8	F/42	+/2 months	18 days	-	-
9	F/25	-	9 months	Multiple sclerosis	-
10	F/42	-	2 months	-	-
11	M/37	+/6 months	20 days	Brucella orchitis	Psychosis, catatonia
12	F/25	-	30 days	-	Depression
13	M/24	-	15 days	-	Delirium

Table 2 - Laboratory findings of 13 neurobrucellosis cases.

Patient no	CSF findings: White blood cells/mm³ (lymphocytes %)	CSF findings: Glucose (mg/dl) (CSF/blood)	CSF findings: Protein (mg/dl)	CSF findings: ADA (U/L)	Blood findings: Wright test	Blood findings: Wright test	Blood findings: White blood cells/mm³ (lymphocytes %)	Culture results
1	30 (70)	45/110	95	4	1/160	1/640	6400 (34)	*B.melitensis**
2	80 (90)	51/105	86	6	1/40	1/320	8200 (42)	*Brucella spp.*‡*
3	20 (100)	40/100	60	3	1/160	1/640**	4500 (40)	*B.melitensis†*
4	120 (100)	38/96	120	10	1/320	1/1280	12000 (34)	*B.melitensis**
5	110 (70)	62/135	135	16	1/640	1/2560	3400 (42)	-
6	150 (80)	26/100	86	14	1/320	1/2560	5420 (45)	*B.melitensis§*
7	50 (80)	30/90	88	18	1/160	1/2560	4640 (52)	*Brucella spp**
8	360 (70)	44/116	75	20	1/1280	1/1280	9400 (50)	*B.melitensis**
9	170 (70)	33/95	129	30	1/320	1/640	6520 (38)	*Brucella spp.**
10	120 (60)	23/98	105	18	1/160	1/640	9460 (42)	-
11	30 (100)	77/110	48	8	1/1280	1/5160	11200 (36)	*Brucella spp.**
12	90 (80)	47/98	53	6	1/160	1/640	7460 (32)	*B.melitensis†*
13	40 (100)	41/100	110	5	1/160	1/640	5640 (36)	-

*CSF culture, †blood culture, ‡lymph node culture, §bone morrow culture
(bone marrow culture was carried out in 4 cases, tissue culture [lymph node] was carried out in one case)
**2 weeks after onset of clinical presentation
CSF - cerebrospinal fluid, ADA - adenosine deaminase, *B.melitensis - Brucella melitensis, Brucella spp - Brucella species*

Table 3 - Complaints, physical examination findings, some imaging findings, and treatment protocols of 13 patients with neurobrucellosis.

Patient no	Symptoms	Physical findings	Imaging findings	Therapy	Outcome
1	Fever, headache, vomiting, epileptic seizure	Neck stiffness, motor deficit 3/5 in upper extremities and lower extremities, epileptic seizure	MRI: hydrocephalus EEG-epileptiform pattern	3 months antibiotic therapy*	Recovered
2	Fever, headache, nausea and vomiting	Neck stiffness, cervical lymphadenopathy	MRI-cranial: N	3 months antibiotic therapy*	Recovered
3	Fever, headache, vomiting, confusion	Neck stiffness, confusion	MRI-cranial: N	3 months antibiotic therapy*	Recovered
4	Fever, headache, confusion, vomiting, inability to walk	Neck stiffness, confusion, splenomegaly, motor deficit 2/5 in upper and lower extremities	MRI-cranial: N	6 months antibiotic therapy*	Recovered
5	Confusion, urinary incontinence	Hepatomegaly, confusion	MRI-cranial: N	6 months antibiotic therapy*	Recovered
6	Fever, headache, muscle weakness	Motor deficit 2/5 right lower extremities	MRI-cranial: N	6 months antibiotic therapy*	Recovered
7	Confusion, urinary incontinence	Hepatosplenomegaly, lack of orientation and cooperation involvement of 7th cranial nerve	MRI-cranial: N	6 months antibiotic therapy*	Recovered
8	Fever, blurred vision, inability to walk	Neck stiffness, involvement of 8th cranial nerve, papilledema, motor deficit 3/5 upper and lower extremities	MRI-cranial: N	9 months antibiotic therapy*, steroids for 4 weeks	Motor deficit upper extremities
9	Fever, confusion, urinary incontinence	Neck stiffness, involvement of 7th-6th cranial nerve, motor deficit 3/5 upper and lower extremities, lack of orientation and cooperation	MRI-cranial: hyperintense demyelinated plaques in the left external capsule, lentiform nucleus and bilateral corona radiata	9 months antibiotic therapy*, steroids for 4 weeks	Gait disorder
10	Fever, headache, muscle weakness and pain in left upper extremity	Motor deficit 2/5 left upper extremities	MRI-spine: myelitis at C2-C7 levels	9 months antibiotic therapy*, steroids for 6 weeks	Recovered
11	Fever, urinary incontinence, muscle rigidity	Neck stiffness, psychosis, catatonia	MRI-cranial: N	9 months antibiotic therapy*, steroids for 6 weeks	Recovered
12	Fever, headache, sleep tendency	Depression	MRI-cranial: N	6 months antibiotic therapy*	Recovered
13	Fever, auditorial hallucination, seeing strange images and occasionally inability to recognize family	Neck stiffness, delirium, increased psychomotor activity, lack of orientation and cooperation, epileptic seizure	MRI-cranial: N EEG-epileptiform pattern	6 months antibiotic therapy*	Recovered

*Treatment protocol was rifampicin, doxycycline, and ceftriaxone for 2 weeks after continued to rifampicin, doxycycline, and trimethoprim sulfamethoxazole until end of the therapy, N - normal

Meningoencephalitis. Patients 1, 2, and 3 had acute meningoencephalitis. They had no complaints until 2 weeks prior. All patients had blood STA ≥1/320. The CSF analysis showed lymphocytic pleocytosis (mean WBC count 43 cell/mm^3, lymphocyte 86%), increased micro total protein (MTP) content (mean 80 mgr/dl), STA ≥1/40, and ADA levels ≤6 u/L (mean 4.3 u/L). Patients 4-8 were treated with the diagnosis of chronic meningoencephalitis added to chronic brucellosis. Findings of meningitis had presented for at least 15 days in all the patients. All patients had blood STA ≥1280. The CSF analysis showed lymphocytic pleocytosis (mean WBC count 158 cell/mm^3, lymphocyte 80%), increased MTP (mean 101 mg/dl), STA ≥1/160 and ADA levels ≥10 u/L (mean 15.6 u/L). Patient 4 had shown serious hyponatremia with serum sodium levels: 115 mEq/l. Syndrome of inappropriate antidiuretic hormone (ADH) was considered because of blood sodium levels, serum and urine density results. The patient recovered dramatically after the treatment.

Cerebral demyelination. Patient 9 had been diagnosed with multiple sclerosis one year earlier and treated with pulse steroid. Also, brucellosis was diagnosed 3 months earlier, however, she was not treated. Cranial MRI revealed hyperintense demyelinated plaques. Steroid was added to the antibiotic therapy for 4 weeks. Her cranial lesions markedly regressed 8 weeks after treatment and improved at the end of the treatment.[4]

Myelitis. Patient 10 was admitted with motor deficit in the left arm and headache. Cervical MRI showed myelitis at the C2-C7 levels. Myelitis signs disappeared after the treatment.

Neuropsychiatric disorders. Patients 11-13 were followed in our hospital with neuropsychiatric picture. Blood STA was ≥1/640. The CSF analyzed was STA ≥1/160, lymphocytic pleocytosis (mean WBC count 53 cell/mm^3, lymphocyte 93%), increased MTP (mean 70 mg/dl) and ADA level ≤8 u/L (mean 6.3 u/L). All patients were cured without sequelae except for patient 8 and 9.

Discussion. Central nervous system involvement in brucellosis has been reported in rates varying between 3-17% in different series.[5-7] In our study, the incidence of neurobrucellosis was 4% and the female/male ratio was 9/4. The incidence of neurobrucellosis was compatible with other studies. Other studies have reported the female/male ratio as 1:2.[6,8] The high ratio of women in our study is due to the fact that in our region women traditionally work to produce cheese from unpasteurized milk and in rural areas women are directly involved in animal breeding. Pathogenesis of neurobrucellosis was probably due to the direct effects of bacteria during the acute bacteremic stage, or it was probably related to the ability of Brucella microorganisms to live within the phagocytes for a very long time, decreased host immunity may allow the organisms to proliferate.[5,8] Neurobrucellosis can affect any part of the central or peripheral nervous system. Diagnosis is generally delayed, appearing with a non-specific manifestation.[8] The probability of culturing the bacteria in a case of acute or chronic brucellosis is said to be between 15-90% depending on the technique used, and it takes a long time.[1] When all these situations are considered, laboratory data should be more practical and support the diagnosis at a high rate. Clinical pictures of all the patients that were not explained with neurological and psychiatric disorders had common characteristics. They were lymphocytic pleocytosis, increased MTP and STA ≥1/40 in CSF, blood STA was found as ≥1/320.

Meningoencephalitis is the most common clinical presentation (69.2%) in this study. However, the small group of patients in our study limited the investigation of the CNS involvement related to neurobrucellosis. Other studies on neurobrucellosis series have also reported meningitis and meningoencephalitis as the most common clinical forms.[5,6] Meningoencephalitis can be seen as the initial manifestation of brucellosis or superimposed phenomenon in a patient who has chronic brucellosis.[8,9] Meningoencephalitis was the initial manifestation of brucellosis in 3 of the 8 patients while others had chronic meningoencephalitis added to chronic brucellosis. Neurobrucellosis was reported to occur at any stage of brucellosis.[8] It should be kept in mind that all the patients can easily be confused with other infectious diseases like encephalitis, tuberculosis, and neurological or psychiatric disorders without infectious origin.[8,10] In addition to epileptic seizures, focal convulsions, respiratory depression and coma can develop during neurobrucellosis.[11,12] Epileptic seizures were observed in patients one and 13. Inappropriate ADH syndrome was diagnosed in patient 4. Persistent hyponatremia and inappropriate ADH syndrome with neurobrucellosis have been reported before.[13] Patient 8 had papilledema and involvement of the 8th cranial nerve, as also reported in other studies.[5,6,13] Patient 9 had demyelinating plaque in the brain. Demyelination due to brucellosis has been reported previously.[5,14,15] Demyelination had been reported to be due to persistent intracellular effects of the microorganism or an immunologic mechanism triggered by infection.[8,13] If serologic tests of brucellosis are not carried out, slightly increased lymphocytic pleocytosis, increased protein content and oligoclonal IgG band in CSF may suggest multiple sclerosis.[8]

Psychiatric disturbances caused by brucellosis show great similarities with functional psychiatric disorders or can mimic many psychiatric disorders. Neurobrucellosis

should be definitely considered in the differential diagnosis in patients with a psychiatric component who do not improve clinically despite anti-psychotic or anti-depressive treatment and who have a history of occasional fever and sweating particularly in endemic regions. Depression was found as the most common psychiatric disorder.[16] The psychiatric symptoms of the patients in our study were depression, psychosis, and delirium. Similar studies have emphasized that brucellosis may lead to psychiatric disorders and these disorders improve with suitable antibiotics without antipsychotic or anti-depressive treatment.[16] One of the rare complications of neurobrucellosis is myelitis. Myelitis and CNS involvement can either be concomitant, or present alone.[10]

The CSF ADA levels may be above average in neurobrucellosis.[17] For this reason, the CSF ADA level may not be a suitable finding in the differential diagnosis of neurobrucellosis from tuberculous meningitis. Radiological examination of our patients revealed hydrocephalus, demyelinating plaques, and myelitis. The possibility of such radiological involvement has been emphasized in similar studies.[5,8,15] It was considered that radiological and cranial nerve involvement were seldom in neurobrucellosis compared with CNS tuberculosis, which is the most important findings in differential diagnosis. Mortality was not seen in any of our patients. However, persistent neurological deficits in patients 8 and 9 were observed despite long treatment durations and physical therapy programs. Early diagnosis is essential to decrease the duration of therapy and complications. Definite criteria on treatment durations were not determined despite standardized diagnostic criteria.[13] Some authors recommend treatment until the patient completely recovers and CSF findings return to normal.[8,13] Also corticosteroids, which are recommended in the treatment of neurobrucellosis can protect the brain from the effects of bacterial toxins and decrease long term complications.[1,13]

Neurobrucellosis should be suspected in unexplained acute onset or chronic neurological and neuropsychiatric disorders, particularly in endemic regions. If neurobrucellosis is suspected, the rate of correct diagnosis is high with blood and CSF serology and CSF analysis.

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