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Clinical Manifestations in 82 Neurobrucellosis Patients from Kosovo

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ABSTRACT

Background: Central nervous system involvement is a serious complication of brucellosis with various incidence and various clinical presentations. **Patients and Methods:** Hospitalized patients in University Clinical Centre, Clinic for Infectious diseases in Prishtina, with laboratory-confirmed brucellosis, were analyzed, a brucellosis-endemic region. Among the 648 confirmed cases with brucellosis during the period 1991- 2013, 82 patients (12.65%) were diagnosed with neurobrucellosis. The clinical manifestations in patients with neurobrucellosis were evaluated and compared with brucellosis patients. **Results:** The major presentations among the brucellosis patients were headache, fever, sweating, nausea, weight loss and arthralgia, while from CNS predominant complains were: headache, vomiting, tremor, low back pain, hearing loss and visual disturbance. The mean age of 82 neurobrucellosis patients was 31.46 years with age distribution 12-71 years, from them 5 (6.1%), younger than 16 years, with a non-significant predominance of women (53.65%). The most common neurological findings were radiculopathies of legs (41.46%) neck rigidity (46.34%), agitation (25,6%), behavioral disorders (18.3%), disorientation (19.5%) and stroke (1.22%). Cranial nerves were involved in 20 of 82 patients (24.4%). Neurological consequences were evidenced in 5 (6.1%) patients. Three patients leave hospital with consequences of peripheral facial paresis, two with sensorineural hearing loss and one with left hemiparesis. Headache, nausea and vomiting and weight loss are significantly ($p<0.001$) more frequent complains in neurobrucellosis patients compare to patients with brucellosis. On the other hand, as regard to the physical findings and complications, meningeal signs and splenomegaly are significantly more frequent in neurobrucellosis ($p<0.01$) whereas the hepatomegaly and lymphadenopathy were more frequent ($p<0.01$) in brucellosis patients. Different significant correlations were observed among specific complains too. **Conclusions:** Our findings in regard to the specific associations of physical and clinical features in brucellosis patients in Kosovo, may serve as an indication for neurobrucellosis. In endemic areas for brucellosis patients complaining in radiculopathies, persistent headache, facial palsy, hearing loss or presenting stroke without risk factors, should be considered for screening for neurobrucellosis.

Keywords: Brucellosis, Neurobrucellosis, Kosovo, Clinical manifestations.

1. INTRODUCTION

Brucellosis is the most common zoonotic infection in the world caused by *Brucella spp.* Brucellosis has global distribution, more than 500 000 new cases occur annually, but it is more common in countries with limited material sources without good standardized and effective domestic animal health programs (1). High risk areas currently are the Mediterranean Basin (Portugal, Spain, Southern France, Italy, Greece, Macedonia, Albania, Kosovo, Turkey, and North Africa), South and Central America, Eastern Europe, Asia, Africa, the Caribbean, and the Middle East (2). The disease is transmitted to humans by direct contact with infected animals and their products of conception and discharges or by consuming infected milk, milk products and, less often, meat (3). Brucellosis can mimic clinically any systemic disease, resulting with delay in diagnosis and increasing rate of complications. Musculoskeletal manifestations are the most common clinical presentations. However, in endemic areas rare presentations like neurobrucellosis should be diagnosed in any patient with focal or nonspecific neurological manifestations (3).

Neurobrucellosis was first reported by Hughes in 1896.

CNS involvement is seen in brucellosis, with an incidence of 0.5–25%, but present a serious complication, and the clinical presentation is quite heterogeneous, including encephalitis, meningoencephalitis, radiculitis, myelitis, peripheral and cranial neuropathies, intracranial and subarachnoid hemorrhage, and psychiatric manifestations (4, 5, 6).

In the literature diagnostic criteria of neurobrucellosis are still under discussions. According to some authors, the diagnosis of neurobrucellosis might be based on clinical neurological symptoms, whereas according to some other authors the diagnosis is based on microbiological and/or biochemical evidence from cerebrospinal fluid (5, 6, 7, 8, 9).

The aim of this study was to report our neurobrucellosis cases, one of the largest series in the literature, 82 patients, and to compare clinical and epidemiological data between brucellosis and neurobrucellosis patients.

2. PATIENTS AND METHODS

In this study we evaluated hospitalized patients with laboratory-confirmed brucellosis in University Clinical Centre, Clinic for Infectious diseases in Prishtina. Among the 648 confirmed cases with brucellosis during the period 1991- 2013, 82 patients (12.65%) were diagnosed with neurobrucellosis. Diagnosis of neurobrucelosis was based in the following criteria: a) compatible clinical picture; b) CSF analysis with lymphocytic pleocytosis (> 16/mm^3); elevated protein content (> 45 mg/dL) and reduced CSF/plasma glucose rate (< 0.50); and c) the presence of one of the following laboratory findings: isolation of brucella from blood, or positive Rapid agglutination (RAT), Coombs tests (titers ≥1/160) and Wright ≥ 1/160 in serum or any value of titer in CSF obtained by the RAT, Wright or Coombs' tests. d) Response to specific chemotherapy with a significant drop in the CSF lymphocyte count and protein concentration. We used a commercial kit (LIOFILCHEM Italy) for the RAT and Wright. Blood culture system (Becton, Dickinson and Company, USA) was used to culture brucella. Gram, India ink and Ziehl-Neelsen stains were routinely carried out on the CSF. From the same samples were done liquor culture for conventional bacteria, tuberculosis, and fungi. CSF was also analyzed for cells, glucose, and protein content. All patients underwent chest radiograph, spine or cranial CT and/or MR scans. In patients with peripheral nerve complains were done EMNG.

Patients are treated with seven different protocols, depending on clinical presentation and severity of the diseases. The duration of antibiotic therapy depends on clinical response, CSF and serological improvement. Clinical manifestations in brucellosis and neurobrucellosis patients were analyzed and compared. Data were evaluated using SPSS version 22.0. Chi-square tests and Pearson Correlation were applied.

3. RESULTS

During 22 years (1991-2013), 648 patients with brucellosis were treated in the Clinic for Infectious diseases. Among them 492 (76, %) had acute onset of illness with impressive systemic toxicity. Of these 648, 82 (12.6%) fulfill upper criteria for neurobrucellosis, 44 were female and 38 were male. Mean age of patients with brucellosis was 29.55 years comparing to neurobrucellosis 31.46 years, with age distribution 12-71 years. In this group 5 (6.1%), was younger than 16 years.

There was no significant difference in the gender percentage. There was no significant difference of the patients living in the rural area compare to those living in urban areas.

Pre-hospitalization duration of symptoms more than one month in neurobrucellosis is found in 51/82 (62.19%), comparing to brucellosis 208/648 (32.09%). Pre-hospitalized antibiotic use was in direct link with duration of symptoms more than one month, patients with neurobrucellosis significantly often was treated with antibiotics compared to brucellosis (Table 1).

	Brucelosis (N=648)	Neurobrucelosis (N= 82)
gender M/F	376/272	38/44
mean age	29.55	31.46
duration of hospitalization	43.46	45.89
living in rural area	531/648	64/82
history of antibiotic use	207 (31.94%)	48(58.53%)**
duration of complains >1 month	208(32.09%)	51(62.19%)**

Table 1. The general characteristics of patients with Brucellosis and Neurobrucellosis. Chi square test; ** (p<0.01)

Complains leading to admission were: drenching sweats, headache, fever and weakness; there are symptoms of damaged organ system also. Headache, weight loss, low back pain, nausea and vomiting, are significantly often found in neurobrucellosis compared to brucellosis (Figure 1).

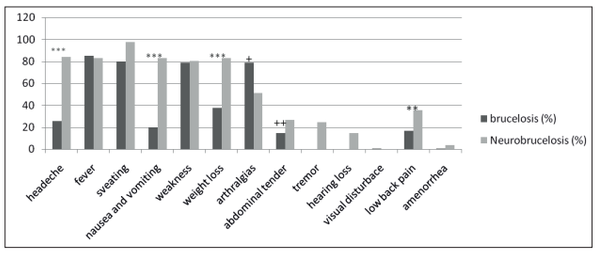

Figure 1. Specific complains in patients with brucellosis and neurobrucellosis (% of patients with the specific complains) (***p<0.001; **p<0.01; +p=0.09; ++p=0.08)

The presence of splenomegaly, radiculopathy and meningeal signs was signs that direct suggest for neurobrucellosis accompanied with cranial nerve damage. Others symptoms and localizations of the diseases doesn't present significance differences between patients suffering from brucellosis or neurobrucellosis (Figure 2).

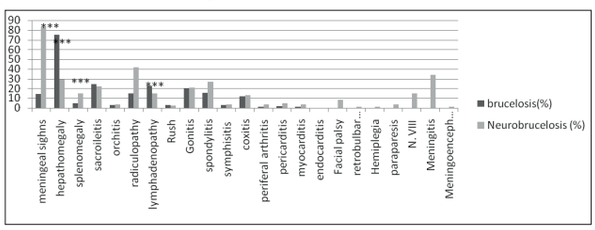

Figure 2. Physical findings and complications in patients with brucellosis and neurobrucellosis (% of patients with the specific Physical findings and complications); ***p<0.001

From 82 patients with neurobrucellosis, osteoarticular involvement was found most often and occurs in 68,12%.

The most frequent was spondylitis (26.8%), sacroilitis (21.9%), gonitis (20.7%) and coxitis (13.4%). Cardiovascular manifestation occurs in 7 patients, 8.5%, 4 with pericarditis and 3 with myocarditis.

Table 2 present clinical presentation and involvement of PNS and CNS in neurobrucellosis.

In our study the most often presentation was affection of PNS in 34 (41, 46%), followed by meningitis 28 (34.14%), cranial nerve damages in 20 (24.39%) and meningoencephalitis in 10 (12,2%). Three had transverse myelitis and one has stroke. The most often affected cranial nerve was vestibulocochlear nerve, 12 (14.63%), facial nerve 7 (8.53%) and n. opticus 1 (1.22%).

	N (%)
Meningoecephalitis	10 (12.2)
Meningitis serosa	28 (34.15)
Radiculopathy	34 (41.46)
Tremor	20 (24.39)
Laesio N. VIII	12 (14.63)
Laesio N.VII	7 (8.53)
Paraparesis	3 (3.66)
Neuritis retrobulbaris	1 (1.22)
Stroke	1 (1.22)

Table 2. Presentations and physical findings in Neurobrucelosis (Nr. 82)

In our study of 82 patients with neurobrucellosis, accompanied meningeal irritation symptoms, and headache was present in 84,1%, fever, nausea-vomiting and positive meningeal signs in 83%, contrary to patients suffering from brucellosis where these symptoms are with lower incidence (Figure 1 and Table 3).

Test	Blood (82)	CSF (12)
	Range	Range
Wright (82)	1/160-1/1280	1/8-1/160
PPD (82)	>6 mm	
Lowenstein (82)	negative	negative
Hexagon TB test (32)	negative	negative
Gene Expert TB (28)		negative
Quantiferon TB gold (12)	negative	negative

Table 3. Laboratory blood and CSF tests

The data from the correlation analysis show some significant correlations for the complains in neurobrucellosis patients: Fever and gender strength of correlation r= 0.43, p<0.01 (the fever is more associated with females); gender and weight loss r= 0.27, p<0.05 (weight loss is more associated with females); fever and vomiting r= 0.31, p<0.01 (more often appear together); fever and weakness r= -0.30, p<0.01 (negative correlation); Arthralgia and vomiting r= 0.34, p<0.01; vomiting and weakness r= 0.22, p<0.05. Other correlation between specific complains didn't show any significance. A comparable average of days of hospitalization was observed.

All patients were negative in screening for TB, based on results from PPD, Culture, Hexagon-TB test, Gene expert TB test, and Quantiferon TB gold, whereas Rapid agglutination (RAT), Coombs tests and Wright from blood was done in 82 patients and in all was positive and only in 12 patients we found positive results from CSF (Table 3).

4. DISCUSSION

CNS involvement of brucellosis is a rare, but important complication. In a number of studies, the rate of neurobrucellosis has been reported at < 5% (4, 8, 9). In our study, this rate was 12.6%. This rate is attributed to the referral of all neurobrucellosis patients to our center since our hospital is a third-level medical center. Some of the non-neurobrucellosis cases are treated in second-level hospitals. In various studies, the male: female ratio has been reported in widely differences as 2:1, 3:2, and 1:2 (1, 5, 7, 8,). In our study, the female : male ratio is considerably low (1:1.15).

Neurobrucellosis can be seen in any stage of the disease, in early acute phase, in convalescence or in recovery phase, presenting in various clinical forms,affecting PNS or/and CNS (3). Therefore, 42 our patients (51,2%) were previously referred to neurology, neurosurgery, ENT, rheumatology or orthopedics. Some authors the most frequent clinical presentations found serous meningitis and meningoencephalitis (5, 8). In our study, the most often presentation was affection of PNS in 34 (41, 46%), followed by meningitis 28 (34.14%), cranial nerve damages in 20 (24.39%) and meningoencephalitis in 10 (12,2%). Three patients were hospitalized as transverse myelitis (3.66%) and one as stroke (1.22%).

In our study accompanied meningeal irritation symptoms, and headache was present in 84,1%,fever, nausea-vomiting and positive meningeal signs in 83%, contrary to patients suffering from brucellosis where these symptoms are with lower incidence.

CSF laboratory findings are not specific for neurobrucellosis, presented as low lymphocytic pleocytosis with low glucose and elevated proteins (4, 5). These CSF finding, in laboratory and clinical confirmed brucellosis patients present an indication for neurobrucellosis whereas EMNG or radiological findings present wide different unspecific changes (5, 15-17).

Diagnosis of neurobrucellosis is usually confirmed by detection of specific antibodies in blood and CSF by ELISA or Coombs' test, or positive CSF cultures with positivity in less than 50% cases (9, 10).

Even the ELISA is latest test than Coombs and is a fast and accurate in diagnosis of brucellosis; in a number of studies ELISA was reported to have no superiority over the Coombs' test (9, 16). Sanchez Sousa et al. found positive anti-brucella antibodies in CSF by the Coombs' test in one patient whose serum test was negative (9). Haji-Abdolbagi et al., in their series of 31 cases, found negative SAT results by Coombs' test in the CSF of two patients and negative results in the serum of two patients (13).

Because neurobrucellosis present wide different clinical picture, no specific radiological and EMNG changes, controversial serological finding in blood and CSF and low positivity of cultures, diagnosis of neurobrucellosisis complex and need to take in consideration all laboratory, epidemiological data and treatment efficacy (1, 5, 9, 15, 16, 17).

In our study, in all 82 patients, we confirmed diagnosis by positive Rapid agglutination (RAT), Coombs tests (titers ≥1/160) and Wright ≥ 1/160 in serum or any value of titer in

CSF obtained by the RAT, Wright or Coombs' tests. Growth in blood culture was observed in 1 (1.2%) cases and no growth from CSF probably due to frequent use of antibiotics before referring to the hospital.

The mortality rate of neurobrucellosis in the post antibiotic era is 0%–5.5%, but permanent neurologic deficits, particularly deafness, are common, 20-30% (15, 18). In our study, we don't evidence any deaths but, 9 patients (10.97%) leave hospital with various sequelae; 3 (3.66%)paraparesis and urinary incontinence, 3 persisting facial palsy (3.66%), two (2.44%) with hearing loss, and one (1.22%) with hemiparesis.

5. CONCLUSIONS

Neurobrucellosis was present with various clinical presentations and specific associations. This disease should always be considered in the differential diagnosis of neurological, rheumatological, ENT and psychiatric cases, in endemic areas for brucellosis. Our findings in regard to the specific associations of physical and clinical features in brucellosis patients, may serve as an indication for neurobrucellosis. Although culture is the gold standard for diagnosis, this method is time consuming and has a low growth rate. Therefore, serum and CSF RAT, Wright and Coombs' tests should be performed, taking into consideration rare serological conditions.

• Conflict of interest: none declared.

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