

OUTCOME OF NEUROBRUCELLOSIS FOCUSED ON TREATMENT

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Abstract

Background: This study aimed to analyze the outcome of neurobrucellosis according to treatment.

Material/Methods: A cross-sectional epidemiologic survey was carried out in 648 patients with brucellosis hospitalized in Infectious Diseases Clinic, UCC of Kosova. Among them 82 patients fulfill criteria for neurobrucellosis and were analyzed regarding medication and outcome.

Results: The mean age of patients with neurobrucellosis was 31.46 years, with age distribution 12-71 years. In this retrograde study the most often presentation of neurobrucellosis was affection of PNS in 34 (41, 46%), meningitis 28 (34.14%), and cranial nerve damages in 20 (24.39%). Radiculopathies of legs (41.46%) was leading finding followed by neck rigidity (46.34%). Clinically in admission patient present agitation (25,6%), behavioral disorders (18.3%) and disorientation (19.5%). Cranial nerves were involved in (24.4%). Five patients (6.1%) leave hospital with severe consequences, three patients with peripheral facial paresis, two with sensori-neural hearing loss and one with left hemiparesis. Leading complains for hospitalization improved in most patients after 6 weeks of treatment, which demonstrated a favorable efficacy. Cross-sectional epidemiologic survey suggested that sex and regional distribution were not related to nervous system damage ($P>0.05$), whereas duration of disease, prior to treatment, were related factor. From a totally 82 patients with neurobrucellosis, 43 patients are treated for 12 weeks, 34 for 24 weeks and 5 for 36 weeks. The shorter duration of treatment without relapses was 24 week.

Conclusions: 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. Based on our data, according to treatment and clinical follow-up, 24 weeks of antibiotic therapy in neurobrucellosis seems adequate. Duration of disease is risk factors for neurobrucellosis.

Keywords: Brucellosis, Neurobrucellosis, Kosovo, outcome

BACKGROUND

Brucellosis is the most common zoonotic infectious disease caused by the *Brucella*. In the early stages of infection, the bacteria invade, as acute febrile illness. *Brucellas* later survive and reproduce in macrophages (HO, 2001). Brucellosis is manifested as acute, subacute or chronic infection damaging multiple tissues and organs (WHO 2011). The disease has global distribution, with more than 500 000 new cases per year, often affecting countries with limited material sources and without good standardized and effective domestic animal health programs (Stevens *et al.*, 2012). High risk areas currently are the Mediterranean Basin (Portugal, Spain, Southern France, Italy, Greece, Republic of North Macedonia, Albania, Kosovo, Turkey, and North Africa), South and Central America, Eastern Europe, Asia, Africa, the Caribbean, and the Middle East (De Sa *et al.*, 2015). CNS involvement is seen in brucellosis, with an incidence of 0.5–25%, presenting as: encephalitis, meningoencephalitis, radiculitis, myelitis, peripheral and cranial neuropathies, intracranial and subarachnoid hemorrhage, and psychiatric manifestations. In the literature diagnostic criteria of neurobrucellosis are still under discussions (Geng *et al.*, 2015).

Because brucellosis is intracellular disease, drugs has limited penetration into cells to kill the bacteria relapses are common. To prevent this, treatment is combined by multiple drugs during acute phase treatment (Scholl *et al.*, 2011)

The optimal treatment duration in patients with brucellosis is still unclear. Combination of tetracyclines for 30–45 days with a 7–21-day course of aminoglycoside therapy (streptomycin or gentamicin) is recommended for symptomatic brucellosis without focal disease (Bothwell *et al.*, 2000) Longer use of antibiotics (6-52 weeks) are recommended in cases with endocarditis, spondylitis, or neurobrucellosis (Romslo *et al.*, 1983).

In this study, the efficacy of the standard treatment regimen was analyzed in 82 patients with neurobrucellosis (NB). Moreover, a cross-sectional epidemiologic survey was conducted in 648 patients with brucellosis to reveal its pathogenic features and risk factors for the development of NB.

METHODOLOGY

In this study we evaluated hospitalized patients with laboratory-confirmed brucellosis in University Clinical Centre (UCC), Clinic for Infectious diseases in Prishtina. Diagnosis was based in the following criteria: a) compatible clinical picture; b) CSF analysis with lymphocytic pleocytosis ($> 16/\text{mm}^3$); elevated protein content ($> 45 \text{ mg/dL}$) 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 $\geq 1/160$) and Wright $\geq 1/160$ 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.

Statistical analysis was performed with SPSS 20.0. Patients with NB and those with brucellosis were compared by t test and Mann-Whitney rank sum test.

Efficacy evaluation: 1. Patients with NB were assessed by the modified Rankin Scale (mRS) [9] at the discharge. 2. For those with intracranial infection and inflammatory demyelination, the efficacy was assessed by clinical symptoms, signs, and lumbar cerebrospinal fluid analysis at admission, and after 2, 6 and 24 weeks of treatment. 3. For those with peripheral nervous system damage, the efficacy was assessed by electroneurophysiological tests at admission, and after 2 and 6 weeks of treatment. Statistical analysis Statistical analysis was performed with SPSS 20.0. Patients with NB and those with brucellosis were compared by t test and Mann-Whitney rank sum test.

RESULTS

During 22 years (1991-2013), 648 patients with brucellosis were treated in the UCC. Acute disease was present in 492 (76, %) with impressive systemic toxicity. From 648 patients with confirmed brucellosis, 82 (12.6%) fulfill criteria for NB, 44 females and 38 males. Mean age of patients with brucellosis was 29.55 years comparing to NB 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 and living origin, comparing rural versus urban areas. Pre-hospitalization duration of symptoms more than one month in NB 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 NB significantly often was treated with antibiotics compared to brucellosis (Figure1).

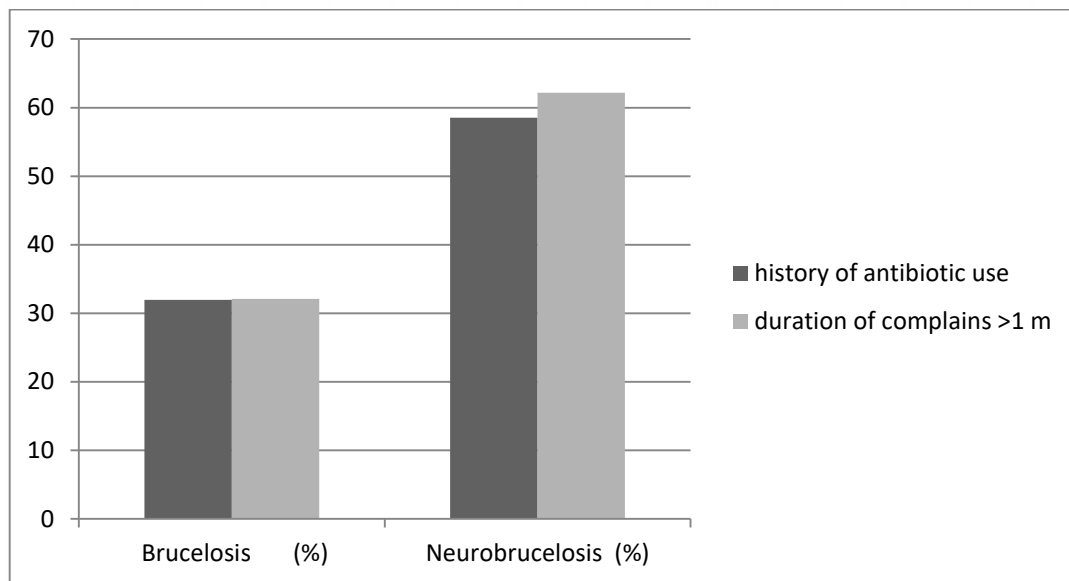


Figure 1. Percentage of the patients with the history of antibiotic use and duration of complains longer than one month among patients with Brucellosis and those with Neurobrucellosis.

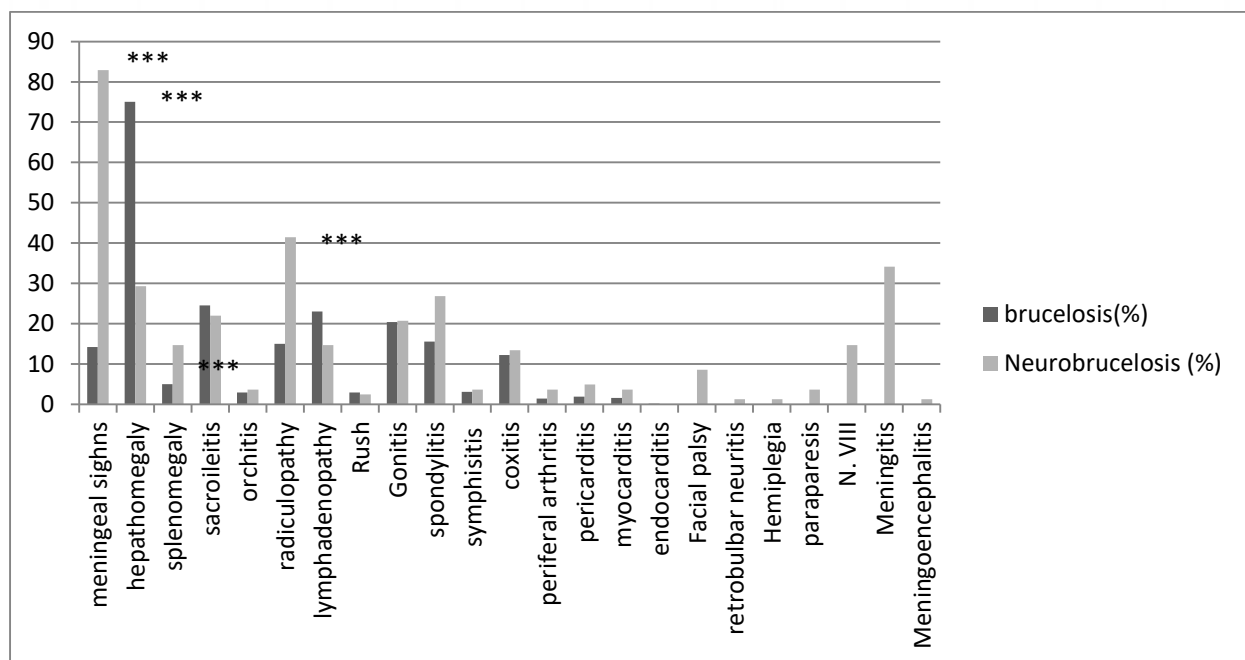


Figure 2. Physical findings and complications in patients with brucellosis and neurobrucellosis (% of patients with the specific Physical findings and complications); ***p<0.001

Headache, weight loss, low back pain, nausea and vomiting, are significantly often found in neurobrucellosis compared to brucellosis (Figure 2).

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

The data from the correlation analysis show some significant correlations for the complains in NB 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. From 82 patients with NB, 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 1. Presentations and physical findings in Neurobrucellosis (Nr. 82)

Meningoencephalitis	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)

In our study the most often presentation was affection of peripheral nervous system (PNS) in 34 (41, 46%), followed by meningitis 28 (34.14%), cranial nerve damages in 20 (24.39%). From a totally 82 patients with NB, 43 patients are treated for 12 weeks, 34 for 24 weeks and 5 for 36 weeks. The shorter duration of treatment without relapses was 24 week.

DISCUSSION

CNS involvement of brucellosis is not often but present important complication. Different studies find different incidence of NB among patients with confirmed brucellosis, from $< 5\%$ to 25% (Moretti *et al.*, 2015, Breymann *et al.*, 2015). In our study, this rate was 12.6% . This rate is attributed to the referral of all NB patients to our center since our hospital is a only third-level medical center for entire country. Because brucellosis is difficult to cure and patients tend to relapse easily (with a relapse rate of 5% to 10% , a long course or multiple courses of treatment with a combination of antibiotics with high cell-wall permeability and strong CNS-penetrating effects should be administered (WHO).

NB 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 (Geng 2015). Therefore, 42 our patients ($51,2\%$) were previously referred to neurology, neurosurgery, ENT, rheumatology or orthopedics. The mortality rate of NB in the post-antibiotic era is $0\%–5.5\%$, but permanent neurologic deficits, particularly deafness, are common, $20\%–30\%$ [13, 14, 15]. In our study, we don't evidence any deaths but, 9 patients (10.97%) leave hospital with various

sequalae; 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.

In this study, the proportion of patients with CNS damage was close to those with peripheral nervous system damage, which might be because the patients with NB admitted to our hospital were severe cases. Since our hospital is the only third level hospital medical center, all critical patients are transferred to our hospital. In this study, analysis confirmed that duration of the disease was risk factor related to the development of nervous system damage in patients with brucellosis. Patients with a longer pre-treatment duration of brucellosis were more likely to suffer from nervous system damage, which is consistent with the findings of a previous published studies (WHO 2011).

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. Based on our data, according to treatment and clinical follow-up, 24 weeks of antibiotic therapy in neurobrucellosis seems adequate, since, among 39 patients treated with four different combinations of antibiotics for 24 weeks, we don't evidence any relapse.

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