Epidemiological and Clinical Features of Brucellosis in Hospitalized Patients in Kosovo

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Citation

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Abstract
Background: Brucellosis is recognized as a clinical and health problem in underdeveloped countries. This research is a descriptive study to present the epidemiological features, clinical aspects and laboratory results of hospitalized patients in the University Clinical Center of Kosova, Infectious Diseases Clinic in Pristina in a six-year period.

Materials and Methods: 124 hospitalized patients with confirmed brucellosis were included in the study. Sociodemographic, clinical, diagnostic and data regarding the treatment were collected from patients' medical records. A serological test was used for diagnosis of the disease.

Results: The mean age of patients was 30.78±17.24 years with a range 2-74 years. 44 (35.5%) of them were females and 80 (64.5%) males, p<0.01. Most affected age groups were 11-20 years old. The highest brucellosis rate was observed in children and students (30.6%). Osteoarticular manifestations were the most common forms of localized disease, which affected 44.45 % of patients. A combination of streptomycin and doxycycline the first three weeks, continuing rifampicin and doxycycline was the most applied treatment protocol.

Conclusion:
The majority of patients with brucellosis in this study were attributed to direct contact with animals. Osteoarticular manifestations were the most common forms of localized disease.

INTRODUCTION
Brucellosis is one of the world's most widespread zoonoses caused by gram-negative bacilli of the genus Brucella (Brucella abortus, B. suis, B. melitensis and B. canis). Brucellosis in humans (mainly caused by B. abortus and B. melitensis), is characterized by continued, intermittent or irregular fever, headache, weakness, profuse sweating, chills, arthralgia, depression, weight loss and generalized aching. In the countries where food hygiene prevents foodborne brucellosis, the disease is largely occupational and the majority of cases are males between the ages of 20 to 45 years. In the populations where food-borne brucellosis is common, such as nomadic societies, children account for a high proportion of acute cases.

Brucellosis in animals presents a subacute to chronic disease affecting a range of domestic and wildlife species and is a leading cause of abortion in livestock. It is a systemic disease that can involve any organ or system of the body. However, the most common manifestation is fever. Human brucellosis usually manifests as an acute or subacute febrile illness which may persist and progress to a chronic form.

Generally, human infection occurs through consumption of poorly prepared meat and dairy products in the form of milk, cheese and butter but can also arise through exposure to animals and carcasses due to occupation. In humans, brucellosis caused by B. melitensis, which mainly causes infection in goats and sheep, is the most clinically obvious. The region of Prizren in southern part of the Kosovo is already an endemic zone and it is anticipated an upward trend of frequency occurrence of brucellosis in coming years. In a large cross-sectional survey of the seroprevalence of brucellosis in sheep, goats and cattle in Kosovo the seropositive animals were found in 25 per cent (19 to 32 per cent) within 162 villages surveyed. Brucella
melitensis predominates as the cause of brucellosis in ruminants in Kosovo\(^9\). Brucellosis is a major concern for most of the countries in the Balkans. In 2008 the incidence in Serbia is reported to be 3.3 per 100 000. In Macedonia, an incidence of 18.6 and 24 per 100 000 was reported in 2007 and 2008, respectively\(^10,12\). In Albania, an incidence of 25 per 100 000 inhabitants was reported in 2008\(^13\). In 2009 in Bosnia and Herzegovina, the incidence increased from 3.8 to 33.43 per 100 000\(^14\).

The cross border migration of people and animals between these countries facilitates the spread of old and creates new zoonoanthropogenic foci of brucellosis in the region. Rural and peri-urban agriculture also carries risks, including that of increased transmission of zoonotic diseases\(^15\). Possible major source of infection with brucellosis might include marketed foods in urban and peri-urban areas, and contacts with animals and home consumption in rural areas.

**MATERIALS AND METHODS**

This is a descriptive study performed on 124 hospitalized patients with Brucellosis at the Infectious Diseases Clinic, University Clinical Center of Kosova in Pristina during the period from January 2006 until the end of December 2011. For each patient, a blood sample was collected and tested by the Wright test. Positive criterion for the Wright was the titer 1/80.

Treatment protocols in our study included: streptomycin 1g/day or gentamycin 3-5 mg/kg daily administered for the first three weeks with rifampicin 15-20 mg/kg (maximum 600-900mg/day) continuing by rifampicin in combination with doxycycline 2-4 mg/kg per day (maximum 100 mg administered orally twice daily for six weeks), or trimethoprim 10 mg/kg per day; sulfamethoxazole, 50mg/kg per day divided in 2 doses. For children the initial combination was gentamycin and trimethoprim/sulfamethoxazole followed by rifampicin and trimethoprim sulfamethoxazole. Efficacy of treatment was determined by rates of failure or relapse with a follow-up period of two years. After treatment, all patients were evaluated at two weeks and 1 month intervals and whenever clinical symptoms reappeared.

**STATISTICAL ANALYSIS**

Statistical analysis of data was performed using SPSS for Windows version 18.0. Descriptive statistics, were used to describe demographic data, and clinical data. Pearson’s Chi-square test was used to compare qualitative clinical data between patients. The t-test was used to compare the age between males and females. A p-value ≤ 0.05 was considered as a significant result.

**RESULTS**

Overall 124 hospitalized patients were included in the study. The mean age of patients was 30.78 ±17.24 years with a range 2–74 years. 44 (35.5%) of them were females and 80 (64.5%) males, p<0.01 (table 1).

<table>
<thead>
<tr>
<th>Characteristics of patients</th>
<th>Male (n=80)</th>
<th>Female (n=44)</th>
<th>Total n=124</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± S.D. (yr)</td>
<td>31.23 ± 17.18</td>
<td>29.98 ± 17.51</td>
<td>30.78 ± 17.24</td>
</tr>
<tr>
<td>Resident</td>
<td>63.0%</td>
<td>58.6%</td>
<td>60.8%</td>
</tr>
<tr>
<td>Urban</td>
<td>28.8%</td>
<td>36.4%</td>
<td>32.3%</td>
</tr>
<tr>
<td>Rural</td>
<td>7.6%</td>
<td>5.9%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Seasonal distribution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spring</td>
<td>24 (30.0)</td>
<td>9 (20.4)</td>
<td>33 (26.6)</td>
</tr>
<tr>
<td>Summer</td>
<td>29 (36.2)</td>
<td>16 (36.4)</td>
<td>45 (36.5)</td>
</tr>
<tr>
<td>Autumn</td>
<td>18 (22.5)</td>
<td>12 (27.3)</td>
<td>30 (24.2)</td>
</tr>
<tr>
<td>Winter</td>
<td>9 (11.3)</td>
<td>7 (15.9)</td>
<td>16 (12.9)</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct contact</td>
<td>49 (61.2)</td>
<td>16 (36.4)</td>
<td>65 (52.4)</td>
</tr>
<tr>
<td>Ingestion</td>
<td>4 (5.0)</td>
<td>10 (22.7)</td>
<td>14 (11.3)</td>
</tr>
<tr>
<td>Without risk factors</td>
<td>27 (33.8)</td>
<td>18 (40.9)</td>
<td>45 (36.5)</td>
</tr>
<tr>
<td>Clinical type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>63 (78.7)</td>
<td>36 (81.8)</td>
<td>99 (79.8)</td>
</tr>
<tr>
<td>Subacute</td>
<td>15 (18.8)</td>
<td>7 (15.9)</td>
<td>22 (17.7)</td>
</tr>
<tr>
<td>Chronic</td>
<td>2 (2.5)</td>
<td>1 (2.3)</td>
<td>3 (2.4)</td>
</tr>
</tbody>
</table>

The mean age of females was 29.98±17.51 years while the mean age of males was 31.23 ±17.18 years, without a significant difference between them. In urban area live 33.1% of patients with a significant difference with rural area where live 66.9% of patients, p<0.01.

Seasonal distribution was highest during summer with 36.3% followed by spring 26.6% of patients. Infection was transmitted in highest frequency by direct contact with animals in 52.4% patients, lowest number by ingestion et11.3% of patients with a significant difference between this to groups, followed by patients with unknown risk factor 63.7%. The disease was acute in 79.8% of the patients, sub acute in 17.7% and chronic in 2.4% of the patients (Table 1).
Patients ≤ 40 years of age account for 75 % of the total hospitalized patients. The highest frequency was observed among the age group of 11-20 year-old patients with a significant difference with other age groups. The mean duration of hospitalization was 28.7 ± 18.7 days (range 2-83). Most affected were pupils and students 30.6% followed by housekeepers 19.4%, farmers and animal husbandry 6.5%, veterinary and veterinary technicians 1.6% (Figure 1).

Table 2
Clinical manifestations in 124 patients with brucellosis

The most frequent clinical sign was artralgia in 86.3% of the patients; sweating 68.6%, fatigue 66.9%, anorexia 58.9% followed by fever 54.8% and restricted joint movement 50.0% in of the patients. Physical findings in abdominal examination include hepatosplenomegaly 26.6%, hepatomegaly 15.3%, and splenomegaly 8.9%. Generalized lymphadenopathy occurred in 27.4% of all patients. Osteoarticular manifestations were the most common form of localized disease which affected 44.45 % of the patients. The largest number of patients (22) had hip synovitis followed by sacroiliitis in 11 patients. Lumbosacral arthrosis was found in 6 patients, hip joint sclerosis in 4 patients and 1 patient had patellar sclerosis. Two patients were found with acute coxitis and 3 with coxarthrosis, 2 with spondylodiscitis, 1 osteomyelitis, 1 with vertebral L4 erosive sclerosis and spondylodiscitis, 1 with Th8-9 erosive sclerosis and 1 with spondylitis and facet arthrosis.

Neurological impairment was found in 2 patients with acute serose meningitis, 2 with sensoro- motoric polyneuropathy and 6 with radicular lesions on the vertebral level L4/5/S1 of middle intensity. Routine chest X ray and auscultation revealed pathologic pulmonary findings in 24% of the patients caused by involvement of Brucellosis, with a dominant rate in male patients with 74%. The radiologic findings revealed pneumonia, bronchopneumonia, paratracheal lymphadenopathy and pleural effusion.

Psychosomatic disorders were diagnosed in 2 male patients and 2 female patients with depressive syndrome. Bilateral conjunctivitis was present in 5.6% of the patients, maculopapulose exanthemas in 5.0%, and jaundice in 3.8%.

One patient manifested thrombosis of VIC, VIE, VFC, VFP, VFS, VP, VSP on the left leg and 1 on the left popliteal vein. Orchiepididimitis was found in 1 patient (Table 2).

Of all124 patients two of them had a co-infection with Tularemia and one with chronic Hepatitis B.

Figure 2
Frequency of antibody titer with serologic method Wright.

Positive Wright tests titer of 1/160 was observed in 7.3% of the patients, 1/640 in 20.96%, 1/1280 in 26.6% , and 1/2560 and 28.2% of the patients. The antibody titer below 1/80 was observed in 1.6% of the patients (Figure 2).
Six (4.8%) patients were also tested by ELISA IgM. One of them tested negative and five of them tested positive for IgM antibodies.

**Table 3**

<table>
<thead>
<tr>
<th>Treatment protocol</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin-Doxycycline-Rifampicin</td>
<td>106</td>
<td>84.5</td>
</tr>
<tr>
<td>Gentamycin-TMP-SMX-Rifampicin</td>
<td>18</td>
<td>14.5</td>
</tr>
</tbody>
</table>

The most applied treatment was streptomycin 1g/day im once or twice daily (children 15mg/kg), rifampicin 15-20 mg/kg maximum 600-900mg/day (children 10-15 mg/kg) and doxycycline 2-4 mg/kg per day, (maximum 100 mg administered orally twice daily for six weeks) et 84.5% of patients, while gentamycin 3-5 mg/kg (children <8 years 1-2.5 mg/kg), trimethoprim10 mg/kg (children <8 years 6-8 mg/kg) per day sulfamethoxazole 50mg/kg per day divided in 2 doses (children <8 years 30-40 mg/kg) was the lowest prescribed treatment protocol et 14.5% (Table 3).

Patients with osteoarticular involvement received medical treatment for at least three months. We performed corticotherapy in 21 patients with osteoarticular complications. For children the initial combination was gentamycin and trimethoprim/sulfamethoxazole for 2 weeks continuing rifampicin plus trimethoprim sulfamethoxazole.

Two of the patients were pregnant patients and treated initially with cephratixon and rifampicin continuing the rifampicin with TMP-SMX. After delivery we tested two years later the patients and the babies which resulted with Wright titer negative.

**DISCUSSION**

The results showed that the majority of patients were less than 40 years (75%) and 64.5% of them were male. The high risk groups includes the active population which is similar with other studies findings 5.

The vast majority of patients live in rural area. A significant number of families in rural communities breed cattle, sheep and goats. This shows that the majority of cases had a history of consumption of dairy products or contact with animal material. Brucellosis is often a disease of rural communities associated with animal husbandry. The prevalence of disease in domestic animals is an important predictor of disease in humans. Brucellosis is more common in men than women 16,17,18. A high proportion of patients in our study (30.6%) were pupils and students followed by housewives and housekeepers, farmers, followed by veterinary and veterinary technicians. Possible explanations of this finding could be a greater risk of exposure amongst boys, with household responsibilities such as shepherding of livestock being preferentially delegated to boys.

The most common brucellosis signs are arthralgia, sweets, fatigue, anorexia, fever, and restricted joint movement.

Osteoarticular involvement, especially hip synovitis and sacroiliitis were the most common form of localized brucellosis. Many authors report similar findings with our study19,20 Hepatosplenomegaly and meningitis were more common among adults while respiratory symptoms were common among young patients. Epididymo-orchitis occurred only in one (1.9%) adult patient21,22,23,24. Neuropsychiatric symptoms were rarely reported in the documentation of the initial presentation of brucellosis, even though many patients had a prolonged duration of infection on presentation. In our study psychosomatic disorders were found in 2.5% and depressive syndrome in 2.5% of all adult patients25.

Almost all patients (81.5%) had an antibody titer higher over 1: 80 and 75.8% of the patients higher than 1:320 measured with the Wright method26. ELISA IgM was used only in 4.8% of patients. As a result, serologic tests with patients' history and disease status were used to diagnosis brucellosis27. Concerning the treatment there are some limitations in choosing the best regimen: there is a limited choice of antibiotics that act intracellular such as doxycycline and streptomycin. The prolonged treatment needed to prevent relapse may increase the occurrence of adverse events (including gastric discomfort, hepatotoxicity, nephrotoxicity, and allergic reactions and reduce adherence to the treatment28. Regimens that combine two or more antibiotics are now recommended by most experts due to high relapse rates with treatment with one type of antibiotic29.

The combination of streptomycin and doxycycline three weeks continuing doxycycline with rifampicin was the most prefered protocol in our study. The relapse rate in our study was 7.3% which is lower than in other studies that used gentamycin-doxycycline regimen30,31,32,33.

A limitation of our study is the use of only one diagnostic test. ELISA IgM was used only in 4.8% of the patients while
the blood culture method was not performed.

CONCLUSION

Brucellosis in this study was mainly attributed to direct contact with animals. Osteoarticular manifestations were the most common forms of localized disease

References

1. WHO: Seven neglected endemic zoonoses - some basic facts. Zoonoses and Veterinary Public Health WHO website; [http://www.who.int/zoonoses/neglected_zoonotic_diseases/en/] website


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