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Human Brucellosis in Tuzla Canton

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Introduction: The prevalence of human brucellosis in Bosnia and Herzegovina and the Tuzla Canton reached its peak in 2008, with a reported total of 994 cases within country, and with 104 cases within the Tuzla Canton. Aim: to analyze the clinical and epidemiological features of human brucellosis in patients hospitalized at the University Clinical Center Tuzla during the period from 01/01/2000 till the 31/12/2010. **Methods**: We retrospectively analyzed the clinical symptoms, the laboratory and X-ray findings, the treatments, and the course and outcome of the disease. The diagnosis of brucellosis was based on anamnesis, clinical presentation, in correlation with a positive blood-culture, and/or serological tests. **Results**: The majority of patients (93.18%) were from rural regions. There were more males (79.54%) than females. Most of the patients were aged between 30 to 39 years (21% cases). Contact with infected animals was registered for 83.40% of the patients. The main symptoms and signs were fever, joint-pains, night sweating, anorexia, headaches, and hepatosplenomegaly. The important laboratory findings were increased erythrocyte sedimentation rates, increased values of C-reactive protein, and anemia. Adult patients were treated with a combination of gentamicin or streptomycin with doxycycline, and the children with a combination of gentamicin, and trimethoprim-sulfametaxasol, over at least 6 weeks. Complications were documented in 20.45% of the patients. Relapses were observed in 14.20%, and a chronic form of brucellosis in 5.11% of patients. There were no cases with lethal outcomes. **Conclusion**: Brucellosis is a growing public health problem, not only within the Tuzla Canton, but throughout Bosnia and Herzegovina. Key words: brucellosis, symptoms, epidemiological characteristics.

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1. INTRODUCTION

Brucellosis is one of the world's major zoonosis, with more than 500,000 patients per year in different parts of the world (1). Brucellosis is primarily a disease of domestic and wild animals, and man is infected by direct or indirect contact with animals through the various modes of transmission (direct contact, inhalation aerosol, foodborne).

The cause of brucellosis are small, gram-negative non-motile, asporogenic coccobacilli.

Brucella is divided into 6-7 species according to the metabolic, cultural, and antigenic characteristics, showing a high homology between the species. B. abortus is found primarily in cattle and other animals (camels, bison); B. melitensis in sheep, goats, and cattle; B. suis in pigs. Brucella can be present in milk, urine and other secretions from infected animals as well as on their skeletons. Brucellosis is often a professional disease amongst cattle breeders, butchers, veterinarians, and laboratory workers. Increasing the interest of the scientific community regarding human brucellosis was initiated by the re-emergence of outbreaks (epidemics), the increased surveillance of brucellosis in many countries of the world, and the fact that Brucella is a bioagent Class B (2).

Brucellosis is a big public health problem in many regions of the world (1, 3, 4, 5, 6, 7). The Mediterranean basin has always had registered cases of brucellosis due to climatic conditions for extensive livestock production in most countries of this region (1, 8).

In Macedonia, the incidence of this disease is very high (44/100,000 inhabitants), and in some regions it even reaches 874,1/100,000 inhabitants (8, 9). Neither Bosnia and Herzegovina, nor the Federation of Bosnia and Herzegovina had higher number of human or animal brucellosis registered till the year 2000, except for 2 sporadic cases (10, 11). The first cases of brucellosis in

Bosnia and Herzegovina were reported after 2000 amongst the owners of donated cattle for refugees who were returning to their homes (12, 13, 14, 15).

The highest number of human brucellosis cases in Bosnia and Herzegovina was registered in 2008, with a total of 994 reported cases (778 cases within the Federation, 216 cases within the Republic Srpska, and 104 cases within the Tuzla Canton) (16). The incidence of brucellosis in 2008 within the Federation of B&H was 33/100,000 inhabitants. At the same time, throughout the whole European Union (EU) fewer cases of brucellosis were registered (735 patients, an incidence of 0.15/100, 000 inhabitants) than in Bosnia and Herzegovina (17).

The data on the occurrence of brucellosis in domestic animals within the Federation of Bosnia and Herzegovina indicate the spread of the disease (172 cases in 2003, 818 cases in 2004, 643 cases during the first half of 2005), with registered cases in the following years also (18, 19, 20). Brucellosis is a systemic disease, and every organ and organ-system can be affected. The particularly severe forms are those cases affecting CNS and the heart. This disease can last for a long time, and if it lasts longer than 12 months it turns into chronic brucellosis (21). Relapses are not uncommon within 3-6 months, especially if the therapy had not been long enough. Chronic brucellosis usually occurs when suppurating inflammatory changes are located within the bones, joints, liver, spleen, or kidneys. A patient with the chronic form is continually febrile, and has a high titer of Brucella IgG and IgA antibodies in the serum.

From the first sporadic cases of human brucellosis treated at the Clinic for Infectious Diseases, University Clinical Center Tuzla, during the period 2000 to 2003 (in total 7 cases) (22) to date, brucellosis has become a serious clinical and medical problem. It was considered useful to present the 11 year period of clinical experiences in the treatment of patients with human brucellosis at the Infectious Diseases Clinic, University Clinical Center in Tuzla.

The aim was to analyze the clinical and epidemiological features of human brucellosis in our hospitalized patients during the period from 1. 1. 2000 to the 31. 12. 2010.

2. PATIENTS AND METHODS

During this descriptive, retrospective study, the official reports on infectious diseases were used from the Department for Public Health at the federal and cantonal levels. The epidemiological, clinical, and laboratory findings were retrospectively collected and analyzed for 176 patients with brucellosis, who were hospitalized at the Clinic for Infectious Diseases of University Clinical Center Tuzla, from the 1. 1. 2000 to the 31. 12. 2010. Data on patients were collected from patient records. The patients were then classified according to the probable place and time of acquiring the infection, their ages, and genders. Their clinical symptoms, laboratory and radiographic findings, and the courses and outcomes of the disease were analyzed in particular. The diagnosis of brucellosis was based on anamnesis, clinical features (basic clinical symptoms and signs), and was correlated with positive blood-culture results and/or any of the relevant serological tests (ELISA, Rose-Bengal agglutination test).

Statistical analysis was performed using descriptive statistical parameters (mean, x value, standard deviation–SD), and comparative methods.

3. RESULTS

At the Clinic for Infectious Diseases of University Clinical Center Tuzla from the 1. 1. 2000 to the 31. 12. 2010 there were a total of 176 patients hospitalized with brucellosis. The largest number of patients were hospitalized in 2008, 79 (44.88%) patients. The lowest number of treated patients was in 2000, 2002, and 2003, only 1 (0.5 patient per year).

The majority of the patients originated from 5 municipalities Tuzla Canton: Srebrenik, Živinice, Lukavac, Kalesija and Tuzla , 138 (78.40%) patients in total. Most of the patients were from rural regions, 164 (93.18%).

Out of the total patients, 140 (79.54%) were males and 36 (20.45%) were females. The majority of patients were within the age group 30-39 years, 37 (21%), and the smallest number of patients, were in the 0-9 years age group 3 (1.7%), (Figure 1). Eleven patients (6.25%) were in the age group 10-18 years. The mean age of the patients was 40.67 years ± 15.36 SD (the youngest patient was 2 months and the oldest 71 years old).

The disease occurred during all months of the year, but more often during the springtime. More patients were hospitalized in April 41 (23.29%), than in May 34 (19.31%), and in June 21 (11.93%). Forty-one patients (23.29%) had previously been treated as outpatients before admission to hospital, and 135 (76.71%) patients were treated exclusively within the hospital. The average duration of the disease before admission to hospital was 37.54 ± 52.4 days. The average time of hospitalization was 21.2 ± 9.2 days. The anamnesis data, the clinical symptoms, and the signs of the disease, are shown in Tables 1 and 2.

Contact with animals was registered for 146 (83.40%) patients. A total of 126 (71.59%) patients bred sheep, goats or cows on small village farms. All these patients gave information about the diseases of any animals they were rearing. There were 11 (6.25%) shepherds, 11 (6.25%) nomads, 4 (2.72%) veterinarians, and 5 (2.84%) veterinary technicians. Data on the consumption of unpasteurized milk or cheese were provided for 10 (5.68%) of the patients. Data on the possible source and mode of infection was in conclusive for 20 (11.36%) patients. Information on brucellosis within the family was obtained from 60 (34.09%) patients.

Fever was observed in 159 (90.34%), weakness in 115 (65.34%), pain in the joints in 104 (59.09%), night sweating in 98 (55.68%), anorexia in 86 (48%), hepatomegaly in 29 (16.48%), and splenomegaly in 7 (3.98%) of patients. Other symptoms and signs registered in the patients are shown in Table 2. Similar symptoms and signs of brucellosis were found in different study in the world, with different frequency (Table 3).

We found different laboratory abnormality in patients with brucellosis (Table 4). Elevated erythrocytes sedimentation (≥ 20 mm/h) was present in 138 (78.41%). Elevated C-reactive pro-

Anamnesis data	Number of patients (%)
Contact with animal	146 (83.40)
Sheeps, goats or cows farming on little country houshold	126 (71.59)
Shepherd	11 (6.25)
Veterinarian	4 (2.72)
Veterinarian technician	5 (2.84)
Consumption of unboiled milk or cheese	10 (5.68)
Unknown	20 (11.36)
Family history of brucellosis	60 (34.09)

Table 1. Anamnesis data in patients with brucellosis

Symptoms and signs	Number of patients (%)
Fever	159 (90.34)
Night sweating	98 (55.68)
Headache	48 (27.27)
Weakness	115 (65.34)
Anorexia	86 (48.86)
Weight loss	37 (21.02)
Rash	3 (1.70)
Cough	24 (13.64)
Vomiting	26 (14.77)
Diarrhea	10 (5.68)
Stomach pain	20 (11.36)
Frequent urination	18 (10.23)
Dysuria	60 (34.09)
Arthralgias	104 (59.09)
One or more swollen joints	4 (2.27)
Myalgias	66 (37.50)
Hepatomegaly	29 (16.48)
Splenomegaly	7 (3.98)
Hepatosplenomegaly	40 (22.73)
Testicular swelling	9 (5.11)
Scrotal redness	1 (0.57)
Scrotal pain	8 (4.54)
Lymphadenitis	3 (1.70)

Table 2. Symptoms and signs in patients with brucellosis

tein (CRP) was found in 116 (65.91%). Leukocytosis was observed in 14 (7.95%), neutrophilia in 11 (6.25%), and lymphocytosis in 36 (20.45%). A decreasing number of erythrocytes were registered in 49 (27.84%), hemoglobin in 115 (65.34%) and platelets in 36 (21.59%) patients. Liver-damage manifesting itself by elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) was noted in 97 (55.11%) and in 66 (37.5%) of patients, respectively.

The diagnosis of brucellosis was based on anamnesis, clinical signs and symptoms, and positive blood-cultures in 48 (27.27%) of patients, a positive ELISA test in 103 (58.52%), and positive from both the Rose Bengal agglutination test and ELISA in 62 (35.23%) cases as shown in Table 5.

Other diagnostic methods like: ECG, ultrasound of the heart, upper abdomen and kidneys; radiological methods (radiography, CT, MRI), were used for diagnosing any complications regarding brucellosis. These complications occurred in 36 (20.45%) of patients, in 32 (18.18%) males and 4 (2.27%) females, respectively.

The following complications were observed: orhiepididimitis in 4 (2.27%), pneumonia in 6 (3.40%), subacute endocarditis of the aortic valve in 2 (1.13%), myocardial infarction in 1 (0.56%), peripheral arthritis in 4 (2.27%), coxitis in 3 (1.70%), spondylitis L/S levels in 4 (2.27%), spondylodiscitis L/S levels in 11 (6.25%), epidural abscess spinal canal L / S level in 3 (1.70%), subdural abscess in 1 (0.56%), and epidural infiltration and infiltration of verterbral body and intervertebral spaces L/S spine in 1 (0.56%).

Complete healing occurred in 142 (80.69%) patients. During the observed period, 25 (14.20%) patients had relapses, whilst 9 (5.11%) developed a chronic form of brucellosis. Antimicrobial therapy was administered according to the standard protocols of the World Health Organization (33)]. Antimicrobial therapies with tetracycline for 6 weeks in combination with gentamicin or streptomycin for 3 weeks, or doxycycline + rifampicin for 6 weeks, were the more prevalent regimes. Gentamicin, in combination with trimethoprim-sulfamethoxazole, over six weeks was used for the treatment of children. The cardiac complications and CNS complications were treated with long-term triple-therapy according WHO recommendations (33). In 4 (2.27%) of patients, besides prolonged antibiotic therapy, surgical intervention was required (for 2 patients with endocarditis and for two patients with spondylodiscitis, vertebral canal empyema). With prolonged antibiotic treatment and, in 2 cases with additional physical treatment, these patients recovered completely.

4. DISCUSSION

We retrospectively analyzed 176 patients with brucellosis who were hospi-

Literature reference	fever (symptom)	malaise	night perspiration	arthralgia	hepatomegaly	splenomegaly
Aygen et al [23]	80	90	84	82	21	14
Yinnon [24]	96	33	ND	35	55	69
Memish et al [25]	91	ND	19	66	6	7
Andriopoulos et al [26]	100	97	96	87	25	51
Shehabi et al [27]	100	ND	88	60	54	61
Demiroglu et al [28]	80	86	78	87	ND	ND
Tasbakan et al [29]	94	96	92	82	38	60
Pourbagher et al [30]	55	76	53	85	6	8
Trujillo et al [31]	100	77	96	81	10	12
Bosilkovski et al [32]	76	68	72	80	50	29
Our study	90	65	56	59	16	4
Abbreviation: ND–not determined.						

Table 3. Frequency of clinical characteristics in patients with brucellosis, reported in our and other studies.

Laboratory findings	Reference ranges	Pathological finding Number of patients (%)	Mean±SD
Erythrocyte sedimentation rate	≤20 mm/1st hours	138 (78.41)	47.57 ± 19.64
C-reactive protein	0.0-3.3 mg/L	116 (65.91)	41.48 ± 42.78
Leukocytes	3.4-9.7x10^9/L	14 (7.95)	10.97 ± 1.28
Neutrophils	44.0-72.0 %	11 (6.25)	75.59 ± 4.71
Lymphocytes	20.0-46.0%	36 (20.45)	53.98 ± 6.54
Monocytes	2.0-12.0 %	28 (15.91)	14.88 ± 2.47
Erythrocytes	4.34-5.72 %	49 (27.84)	4.02 ± 0.31
Haemoglobin	138-175 g/L	115 (65.34)	123.14 ±10.74
Thrombocytes	158-424x10^9/L	36 (21.59)	116.08 ± 33.71
Aspartate aminotransferase	15-37 U/L	97 (55.11)	86.85 ± 65.54
Alanine aminotransferase	30-65 U/L	66 (37.5)	131.38 ± 103.11

Table 4. Laboratory findings in patients with brucellosis

talized at the Clinic for Infectious Diseases, Clinical Center Tuzla, during the period from the 1. 1. 2000 to the 31. 12. 2010. The patients in this study were residents of the Tuzla Canton, within the Federation of Bosnia and Herzegovina. Tuzla Canton is one of the most populated regions in country, with 505,000 inhabitants and 13 municipalities. Human brucellosis was registered in 12 out of the 13 municipalities of Tuzla Canton. The increase in brucellosis cases in Tuzla Canton, especially in 2008, was similar to the increase of brucellosis in other parts of Bosnia and Herzegovina. In 2008, the highest incidence of human brucellosis, 63.37 per 100,000 inhabitants, was registered within the Zenica-Doboj Canton. In the same year, the ratio of incidences within the whole of Tuzla Canton was 20.89 per 100,000 inhabitants. There were no registered cases of brucellosis within the Posavina Canton, Bosnian Podrinje Canton and West Herzegovina Canton (11). In Bosnia and Herzegovina, brucellosis was almost an unknown disease until 2000. During the war in Bosnia and Herzegovina the local livestock was significantly depleted, and there was also a substantial migration of animals from different regions. After the war a large number of cattle, sheep, and goats were imported from different parts of Europe, without any rigorous veterinarian inspections and/or border controls (18). As a result, there have been numerous infectious diseases, of which the most important has been brucellosis. Reports from around the world suggest that brucellosis in many countries had come through the uncontrolled importation of animals, which were never or very seldom tested for the presence of infection (34). Similarly to previous reports from 2008 (22), the majority of patients with brucellosis were registered within the five municipalities of Tuzla Canton: Srebrenik, Živinice Lukavac, Kalesija and Tuzla, with a total of 138 (78.40%) of patients. Reports worldwide also showed that, in some countries, brucellosis occurred more often within specific regions (8, 9, 35).

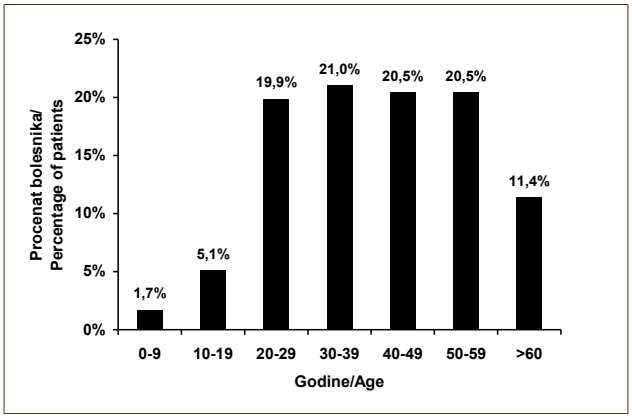

Figure 1. Age distribution of patients with brucellosis

Diagnostic tests	Number (%)
Number of patients with positive RBP test	9 (5,11)
Number of patients with positive ELISA test	103 (58,52)
Number of patients with positive RBP and ELISA test	62 (35,23)
Number of patients with positive blood culture results	48 (27,27)

Table 5. Microbiological characteristics in patients with acute brucellosis

Men were more often infected than women (78.40%), and this result was similar to other reports from Bosnia and Herzegovina (11, 13) as well as other parts of the world (23, 28, 32). Between the ages of 0-18 years there were 11 (6.25%) patients, similar to reports from worldwide (21, 36, 37). Data on the seasonal appearance of the disease during springtime and its lambing ewes were reported in other studies (4, 5, 9). The majority of patients were breeders of sheep, goats or cattle on small rural farms. In our study, sheep were the most common source of the disease amongst humans, as well as in other parts of Bosnia and Herzegovina (12, 13, 14). Majority of patients, 93.18%, were from rural regions. Brucellosis is an occupational disease (9, 23, 30, 32). In 34.09% of our patients, brucellosis was registered amongst family members, similar to other study in the world (25). Human brucellosis is the growing health problem in Bosnia and Herzegovina and in the last 11 years it has become endemic in many parts of our country.

Data about the times of admissions, and diagnoses, and the initiation of adequate treatment in our previous report of 2008 (22), suggested that the patients arrived relatively late in the ambulance and the diagnosis of disease was untimely. The average incidence of this disease before hospital admission in 2008 was 20.6 ± 19.9 days. In this presented report, the illness had lasted for 37.54 ± 52.4 days before admission, thus confirming our findings that the diagnoses of the disease and its treatment were delayed. It is necessary to bear in mind that brucellosis is an endemic disease in Bosnia and Herzegovina, and that comprehensive and targeted epidemiological history may direct diagnostic procedures that confirm the etiology of the disease. The clinical symptoms and signs of the disease are similar to numerous reports

worldwide (Tables 2 and 3). The leading symptoms were fever in 90.34%, weakness in 65.34%, arthralgia in 59.09%, and night sweating in 55.68%. Laboratory findings in our patients did not differ from the findings reported in the patients of other studies (SE moderately elevated, anemia, leukocytosis initially and then later leucopenia with lymphocytosis, and non-specific reactive hepatitis with elevated serum transaminase) (6, 23, 32). Clinical symptoms and signs, laboratory findings, and other diagnostic techniques (radiography, ultrasound, CT, MRI), suggested moderate to severe brucellosis. Patients with mild forms of brucellosis refused hospitalization and were treated as outpatients.

Based on various clinical and routine laboratory tests, it is difficult to diagnose brucellosis. Diagnosis is established by isolating Brucella bacteria from blood, bone-marrow, and other tissues (3, 21). The number of our patients with positive blood-cultures, 48 patients (27.27%), was similar to data worldwide. According to these data, the percentage of positive blood-cultures ranged from 15-70% (3). The disease in all patients was confirmed either by positive blood-cultures, and/or serology (Rose Bengal-agglutination and ELISA). Lately, a greater need has arisen for the molecular diagnosis of brucellosis, especially in unclear clinical and laboratory cases. Polymerase chain-reaction has great advantages over traditional bacteriological methods, having higher sensitivity, and significantly faster results.

Clinical presentations of brucellosis vary from very mild to severe. The severe form of brucellosis with numerous complications, but rarely with fatal outcome, has been described in numerous reports worldwide (3, 25, 29, 32). In our country there have been no registered fatal outcomes of the infection. Within the presented period, 14.20% of patients had relapses, whilst 5.11% of patients developed chronic forms of brucellosis, similar to study from other parts of the world (5, 23, 28, 32).

The therapy was carried out using two or three of the antibiotics recommended by the WHO (33). For the long-term treatment of neurological and cardiac complications, three antibiotics were used according to WHO recommendations (33). Some of our patients (23.29%) received different antibiotics before admission to the hospital, which could have affected a correct diagnosis of brucellosis, and the final outcome. The therapy we applied for our patients was effective for a high-percentage. However, for better efficiency and the prevention of developing chronic forms, treatment should be carried-out long enough and never with a single antibiotic. Sometimes the treatment needs to be individually modified. For some complications (neurological, cardiac), antibiotic therapy should be combined with surgical therapy in some cases.

Since brucellosis is a disease of high medical, economic, and public-health importance, it is very important which strategies are used to control brucellosis. Brucellosis in Bosnia and Herzegovina and the Tuzla Canton is not just a health problem alone and it required activity different sectors. The animal and epidemiological service of Tuzla Canton was actively involved during the entire epidemic occurrence of brucellosis. Although significant progress in controlling brucellosis was made in comparison with the previously reported period, there are still problems relating to the lack of national strategies for the prevention of brucellosis, animal trafficking, migration, at the Country level.

5. CONCLUSIONS

Brucellosis in Tuzla Canton, as well as throughout the whole of Bosnia and Herzegovina, is a serious but not just a health problem. Brucellosis in the studied patients was presented in different clinical presentation, imitating many other diseases, rendering it without epidemiology data and microbiology diagnostic very difficult to diagnose.

The time of diagnosis and the initiations of adequate therapy in the observed patients of this study suggest that the patients arrived quite late at the clinic and thus the diagnoses and treatment were untimely. This study showed that the WHO's therapeutic algorithms were successful when treating the patients. However, due to 14.20% cases with relapses and 5.11% of cases with chronic brucellosis, it is necessary to stress the importance of treatment durations, which should be strictly implemented based on WHO recommendations.

In order to establish better control of brucellosis within Bosnia and Herzegovina, it is crucial to adopt and implement unique national multidisciplinary strategies for the diagnosis, treatment, and prevention of animal and human brucellosis by close collaboration between human and animal medicines.

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