

Original Article

The role of gender in the prevalence of human leptospirosis in Albania

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Abstract

Introduction: Leptospirosis is a zoonotic spirochetal disease with global importance, which continues to have a major impact on public health in developing countries. The prevalence of the disease is much higher in males. The objectives of this study were: to give some data and to share our experience with human leptospirosis in Albania; to describe the prevalence regarding to the role of gender in the prevalence of human leptospirosis; to make a gender specific analysis of the clinical manifestations in patients diagnosed and treated for leptospirosis in our service and to make a review of literature related to this hypothesis.

Methodology: We reviewed the epidemiologic data, risk factors and differences in clinical presentation between males and females' patients with leptospirosis. These data are analysed from hospitalized patients. Diagnosis of leptospirosis was established based on clinical presentation, epidemiological data and subsequently confirmed serologically by Anti-*Leptospira* IgM antibodies through ELISA test.

Results: Between 2005-2016, 233 cases of confirmed leptospirosis were analysed. Males were 208 (89.27%) and 25 of patients (10.72%) were females in ratio 9:1 $p < 0.001$. The highest prevalence was observed in the 45-64 age groups. Overall mortality was found to be 8.58%, 19 were males and one female $p < 0.001$.

Conclusions: There is a much higher prevalence of leptospirosis in middle aged men. Mortality rate seems to be similar in males and females. While the difference in prevalence may be related to exposure to risk factors, further investigation is necessary to study gender-based genetic and immunological predisposition.

Key words: leptospirosis; zoonosis; gender; males; immunity.

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Introduction

Leptospirosis is a re-emerging disease with worldwide distribution, with higher incidence in the developing world [1–4]. The disease is encountered in both urban and rural settings in countries with tropical, subtropical, or mild climate. Leptospirosis is caused by pathogenic species of *Leptospira*, after direct or indirect contact with urine of infected animals [5,6]. The disease is endemic in humid, tropical, and subtropical areas of the world, where most of the developing countries are located. Rodents are the main natural reservoir of the bacteria, but certain herbivores can serve as a reservoir, too [1,3,7–10]. As a zoonosis, leptospirosis is encountered in different epidemiological settings, but the most affected groups are patients from a lower socio-economical level [8–10]. Occupations more associated with leptospirosis are farming, fishing and automotive repair [11]. Being a male is a major risk factor as well as being between the ages of fifteen to

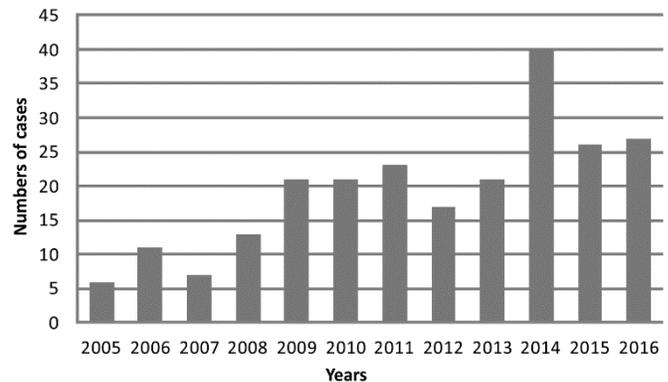
sixty-four. Many studies have pointed out the significant difference in incidence between males and females [3,12–15]. This commonly cited risk factor is observed mainly in surveillance data and is often attributed to increased occupational exposure associated with male gender. However, it is unknown how this observed distribution reflects on the disease severity [12]. Based on previous reports the gender ratio for leptospirosis in Albania goes as high as 1:8 in favour of the males [3]. Although different studies have shown different ratios, there is a major body of literature that demonstrates a higher incidence of leptospirosis in males worldwide [16–28]. The goal of this study is in four points: to give some data and to share our experience with human leptospirosis in Albania; to describe the prevalence regarding to the role of gender in the prevalence of human leptospirosis; to make a gender specific analysis of the clinical manifestations in patients diagnosed and treated for leptospirosis in our

infectious diseases service during January 2005-December 2016 period and to do a review of literature related to this hypothesis.

Methodology

Leptospirosis is a reportable disease in Albania. In this study we used the data of patients hospitalized in our infectious diseases service and data from Albanian Institute of Public Health. Our hospital is the only tertiary service for infectious diseases in Albania, so the main infectious diseases like leptospirosis are treated in it. All patients above the age of 14 were included. In each case, leptospirosis was diagnosed based on clinical, epidemiological, and laboratory data, including specific *Leptospira* serologies. Serologic examinations were performed at the IPH (Institute of Public Health) laboratory, which is also the local reference laboratory centre for infectious diseases. The serologic diagnosis of leptospirosis was confirmed by ELISA, IgM and the IgG as microscopic agglutination test (MAT) is not available in Albania [3]. For each patient, 5 mL of blood was obtained and stored at -20° Celsius until the test was performed. For each sample IgM, ELISA (Institute Virion/ Serion GmbH, Warburg, Germany) was done. For this kit the result interpretation is as follows: anti-leptospira IgM < 15 IU/mL is considered and suggests that there is no acute infection, anti-leptospira IgM 15–20 IU/mL is considered borderline raising the possibility of acute infection and anti-leptospira IgM ≥ 20 IU/mL is considered a positive result indicating acute infection with *Leptospira*. Patients were classified according to the following age categories: 15-24, 25-34, 35-44, 45-54, 55-64 and ≥ 65 year. Chi-square statistical analysis was used and a value of p < 0.05 was considered to be statistically significant.

Figure 1. Leptospirosis cases from 2005- 2015.



Results

Between January 2005 to December 2016, 233 cases of confirmed leptospirosis were analysed. Males were 208 patients (89.27%) and female were 25 patients (10.72%) in ratio 9:1 p < 0.001. The average age of the patients was 45.36 years (range 17-78). The average time from the initial symptoms until they presented to hospital was 6.8 days. The highest prevalence was observed in the 45-64 age groups. Cases with leptospirosis were seen throughout the year, but most of the cases were presented during spring and summer months. The majority of them (>70%) were coming from rural areas of Albania. The incidence seems to have increased in the last five years as demonstrated on Figure 1. The capital city of Tirana had 38.8% of the cases. Beside Tirana, even in other provinces of the country such as Shkodra-Lezha and Fier-Lushnja, there has been a high incidence. The most common symptoms are fever along with headache, myalgia, vomiting, conjunctival suffusion, jaundice, and diarrhoea Table 1. What was noticed in this study was

Table 1. Clinical symptoms at presentation.

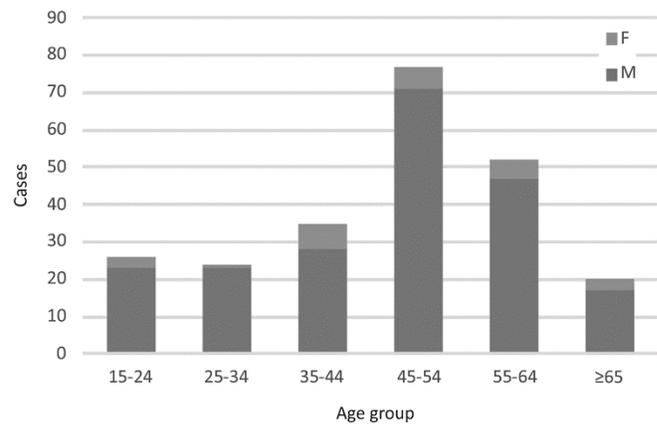
Clinical Symptoms	Male		Female		Total	
	Cases	%	Cases	%	Cases	%
Number of cases	208	89.2	25	10.7	233	100
Malaise	199	95.6	20	80.0	219	93.9
Fever	193	92.7	19	76.0	212	90.9
Myalgia	192	92.3	18	72.0	210	90.1
Conjunctivitis	172	82.6	9	36.0	181	77.6
Icterus	130	62.5	13	52.0	143	61.3
Nausea/vomiting	118	56.7	9	36.0	127	54.5
Headache	111	53.3	10	40.0	121	51.9
Oliguria/anuria	88	42.3	6	24.0	94	40.3
Respiratory symptoms	87	41.8	5	20.0	92	39.4
Abdominal pain	63	30.2	7	28.0	70	30.0
Encephalitis/meningitis	0	0	1	4.0	1	0.42
Mortality	19	9.1	1	4.0	20	8.58

the difference between the two genders Figure 2. For females the average period from the first symptoms until the day of the hospitalisation was 5.36 days, while at males it resulted to be 7.1 days. Overall mortality was found to be 8.58%, 19 were males and one female $p < 0.001$. Mortality among female patients was 4% (1/25), whereas for males was 9.1% (19/208) with statistically significance $p < 0.001$.

Discussion

Leptospirosis is a potentially fatal zoonosis with a worldwide distribution, endemic in tropical regions that can even cause epidemics after rainy seasons [2,14,15,20,22,23]. The incidence of human leptospirosis has increased from 0.2 cases /100 000 people in 2005 to 1.0 cases /100 000 in 2015. It is a disease caused by *Leptospira*, a Gram-negative aerobic bacterium belonging to the Spirochaetaceae family [1,2,4,7,29–31]. Seroepidemiological surveys carried out by the Institute of Public Health (IPH) in the period 1980-1990 in Albania have demonstrated a predominant circulation of species, *Leptospira Pomona* and *Leptospira ichterohaemorrhagica* [11]. The majority of cases are seen between April to September [3,32]. The incidence of leptospirosis has shown a tendency to increase secondary to global demographic changes, climates changes, natural catastrophes and floods [33]. The risk of leptospirosis in Albania during the rainy season becomes higher after flooding that accompanies natural disasters when the human population may be exposed to water contaminated with urine from infected animals. Many outbreaks of leptospirosis occur in urban slums where some of the world's most deprived and vulnerable people live, where socioeconomic resilience is invariably poor, where access to health care is usually already inadequate and where public health services are often limited [3,25,34]. It has been shown that people who are engaged in agriculture and animal husbandry have higher risk of leptospirosis in comparison to other occupations [16,18,22,23,35,36]. Maybe climate changes that are occurring around the world and in our country as well, explain the increased number of suspicious [37]. During the past few years in Albania, the annual rainfall has increased a situation which has been accompanied with floods. Cases have a diverse geographic distribution, but it is the western part of the country which has the highest number [3]. During floods, the infectious agent spreads and reaches distant areas under the impact of water [21–27,33]. The most cases in Albania are reported from Tirana, the capital city [3,37]. This can be explained by the fact that 1/3 of

Figure 2. Distribution by age groups and gender.



Albanian habitants live in Tirana. The highest incidence of leptospirosis was seen in Shkodra-Lezha region that presented a stable trend from 0.3 to 0.5 cases/10.000 population. The provinces of Shkodra and Lezha, have multiple large fresh water sources, including 3 major rivers that have caused floods in both urban and rural areas in recent years. Same thing can be said for Lushnja and Fier, whereas certain areas in the suburbs of Tirana are crowded.

In our patient group the male to female ratio was found to be very high. The preponderance of leptospirosis in males is in agreement with the finding of other workers. The clustering of the disease in people in their 45s and 65s looks reasonable as people from these age groups are more involved in agriculture and animal rearing and hence are more likely to be exposed to risk factors associated with leptospirosis [1,16,17,22,34,35]. Certainly males tend to be more engaged in certain occupations that increase exposure to leptospirosis such as fishing, automotive repair etc. Farming is another important predisposing factor, and we can say that in Albania both males and females are engaged almost equally in farm work [3,11,37,38]. People on rural area were the most affected ones with the 68.4% of total cases. Based on their profession, 63.5% of the patients were farmers, 10.1% fishermen, 7,2% were drivers or auto repair mechanics, and the rest employed in miscellaneous jobs (construction worker or municipal, retired and unemployed) [3,11,32,37,38]. Exposure to animals could be a potential risk factor for the disease. Contact with contaminated soil with rats' urine surrounding home was found to be highly associated as an independent factor [14,24,26,39]. Auto repair mechanics was an interesting finding in this study. That can be explained by the fact that their manufactories are in peripheries of cities, and they have been in contact with animals [3,37,38]. In rural regions

of Albania the exposure to rodents is probably similar between males and females. Traditionally, the increased risk for leptospirosis in males has been explained by the increased occupational or recreational exposure to predisposing factors, especially dirty water and animals [22,23,25]. According to Haake *et al.* people in contact with animals are more likely to being exposed to *Leptospira*, including: veterinarians, slaughterhouse workers, milking workers, hunters, scientists that work with animals in laboratories or in nature [1]. In Albania, milking workers are almost exclusively female. Suut *et al.* report that 59.5% of patients positive for leptospirosis in their study from Malaysia were women [24]. Frequently, the infection is asymptomatic and can be diagnosed only after specific *Leptospira* serologies [23]. Leptospirosis clinical manifestations range from flu-like syndrome to severe forms. Generally, it manifests as an unspecific acute febrile illness, characterized by fever, myalgia and headaches and can be misinterpreted as other diseases, especially on the first days of clinical signs [1,5,14,20]. The most common symptoms are fever along with headache, myalgia, vomiting, conjunctival suffusion, jaundice, and diarrhoea Table 1. In our study it is observed that the patients have been presented to the hospital 6.8 days after the first clinical symptoms. This is an indicator that these patients have been presented at an advanced stage of the illness. From the statistic data it was noticed that the average period that female patient have been presented at the hospital was 5.36 days, while at males it resulted to be 7.1 days. Despite the limited number of patients, it is shown that there is a tendency that the illness is not as much aggressive at females. As the antibiotic treatment and the supportive therapy are to be concerned there were not any significant data that could explain the progress of the illness. If untreated, the illness can progress rapidly and mortality rates can be high in severe cases [31]. In this study the overall mortality was found to be 8.58%, 19 were males and one female $p < 0.001$. Maybe this statistic data can be related to earlier presentation for medical treatment or to another factor, which we will try to analyse below.

Traditionally, the association between being a male and leptospirosis has been explained by the fact that males are usually more exposed to water, and are more likely to engage in occupational or recreational activities that predispose to leptospirosis. However, we want to raise the hypothesis that other gender related genetic, hormonal, or immunological factors may play a role in human leptospirosis. Sex differences in infectious diseases are common, but often neglected especially by males who are more susceptible than

females. This male bias has been documented for bacterial, parasitic and viral infections such as tuberculosis, leishmaniasis and leptospirosis [9,28,34,40]. Giefing-Kröll *et al.* emphasised that later in life probably due to socioeconomic behaviour, such as higher pathogen exposure during agricultural or occupational activities, men are more susceptible to many infections caused by viruses, bacteria, parasites, and fungi. They are significantly more predisposed especially to environmental and vector-borne diseases such as leptospirosis (from 3.5- to 4-fold increased incidence) [28]. Gender differences in immunity, affecting both the innate and the adaptive immune responses, contribute to differences, between males and females, in the pathogenesis of infectious diseases [41]. Several studies have addressed human male-female differences in overall mortality [40]. Other studies before us have shown a very large difference between genders in Leptospirosis incidence. For example Yanagihara *et al.* describe 840 hospitalized patients from the Philippines, between 1998-2001, where 87% of them were males [24]. Similarly, another study from New Zealand reports 878 cases, between 1999-2008, where 88% were males [25]. Jansen *et al.* in a study about leptospirosis in 1997-2005 emphasises that 78% of the patients who had been studied resulted to be men [42]. Guerra-Silveira *et al.* as well, in his study where he mentioned some infective diseases points out that there are obvious differences at adults according to leptospirosis [40]. Based on our own experience, we believe that there might be other factors that may contribute to an increased incidence, and likely a more severe clinical presentation, making them more likely to seek medical attention. In this study the majority of patients were males (male to female ratio was about 9 to 1), who also tended to have a more severe clinical presentation. Giefing-Kröll *et al.* suggest that probably due to socioeconomic behaviour, such as higher pathogen exposure during agricultural or occupational activities, men are more susceptible to many infections caused by viruses, bacteria, parasites, or fungi, and they are significantly more predisposed especially to environmental and vector-borne diseases such as leptospirosis [28]. More recently, certain biological differences have been cited as possible factors that would provide an alternative explanation for the gender related differences observed in leptospirosis. In some European studies, it has been shown that in terms of seroprevalence, there is no significant difference between the two genders, despite the much higher incidence of clinical leptospirosis in males [25]. For example Wasinski *et al.* did not find a significant

difference in *Leptospira* serologic prevalence between the two genders [26]. Esquivel *et al.* concluded that *Leptospira* IgG ELISA seroprevalence was similar between males and females in their study as well [22]. According to Kawaguchi *et al.* when adjusted to risk factor for leptospirosis such as walking and swimming, males are still significantly associated with higher seropositivity [12]. So we can say that there is a significant body of evidence that may suggest that the contact with *Leptospira* may not be different between the two genders, yet the clinical incidence is. According to Caruso *et al.* there is evidence to support that there is a difference in immune response to *Leptospira* in males and females. A sexual dimorphism in the immune response means that females are more resistant to infections [27]. It has been proposed that the differences in host immune responses can lead to disparate disease outcomes, however, the mechanisms involved are far from being established [22]. It is possible that certain genetic factors that can determine the difference in the immune response between male and female may be X chromosome linked, since it is well known that some genes involved in immunity map in this chromosome [9,41].

The limitations of this study include the small number of cases and the only cases to have been included in the study are the cases that have been hospitalised. We do not have information about the cases which have been in contact with *Leptospira* and have not been presented for medical treatment. The fact that the information used was only the one of those patients that exhibited symptoms and that went to a health center may bias some conclusions. We use of single serum sample for ELISA test, because we cannot perform MAT in Albania. It is important to specify that the data was not random. However, we believe that the result of this study depicts the general features of the disease in Albania. Unfortunately, could not manage to make a hormonal or genetic panel to the patients being part of the study.

Conclusions

Leptospirosis is a zoonosis with worldwide distribution, affecting more the developing countries in the tropical and subtropical regions. In limited resource countries like Albania where laboratories could not perform MAT or cultures, serological tests like ELISA can be helpful in early diagnosis of the disease. Although there is a clear correlation between being a male and developing clinical disease, factors that predispose to this correlation remain unclear. We believe that gender-based, increased occupational or

recreational exposure cannot fully explain this difference. There is still a lack of information on sex-associated immune responses in humans and on the interaction between sex hormones and immune cells in infectious diseases. Larger cohort studies are needed in order to evaluate gender based differences in biological and immunological response to *Leptospira* and their role in clinical presentation. Thus, further epidemiologic studies on diseases with a suspected gender bias are necessary and should include immunologic investigations.

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