Gender Disparity between Cutaneous and Non-Cutaneous Manifestations of Lyme Borreliosis

Franc Strle1, Gary P. Wormser2*, Paul Mead3, Kanthi Dhaduvai2, Michael V. Longo2, Omosalewa Adenikinju2, Sandeep Soman2, Yodit Tefera2, Vera Maraspin1, Stanka Lotrič-Furlan1, Katarina Ogrinc1, Jože Cimperman1, Eva Ružič-Sabljić4, Daša Stupica1

1 Department of Infectious Diseases, University Medical Center Ljubljana, Ljubljana, Slovenia, 2 Division of Infectious Diseases, New York Medical College, Valhalla, New York, United States of America, 3 National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Fort Collins, Colorado, United States of America, 4 Institute for Microbiology and Immunology, Medical Faculty Ljubljana, Ljubljana, Slovenia

Abstract

Cutaneous manifestations of Lyme borreliosis in Europe include erythema migrans (EM) and acrodermatitis chronica atrophicans (ACA); the most common non-cutaneous manifestations are Lyme neuroborreliosis (LNB) and Lyme arthritis. The purpose of this study was to evaluate the gender distribution of patients with these clinical manifestations of Lyme borreliosis. Data on gender were obtained from the clinical records of patients with Lyme borreliosis aged ≥15 years who had been evaluated at the University Medical Center Ljubljana, Ljubljana, Slovenia. Among 10,539 patients diagnosed with EM, 6,245 (59.3%) were female and among 506 ACA patients 347 (68.6%) were female. In contrast, among the 60 patients with Lyme arthritis only 15 (25%) were female (p<0.0001 for the comparison of gender with EM or ACA) and among the 130 patients with LNB only 51 (39.2%) were females (p<0.0001 for the comparison of gender with EM or ACA). Although the proportion that was female in the LNB group was greater than that of patients with Lyme arthritis, this difference did not reach statistical significance (p = 0.10). Although older individuals are more likely to be female in the general Slovenian population, the age of patients with cutaneous versus non-cutaneous manifestations was not the explanation for the observed differences in gender. In conclusion, patients with cutaneous manifestations of Lyme borreliosis were predominantly female, whereas those with non-cutaneous manifestations were predominantly male. This provocative finding is unexplained but may have direct relevance to the pathogenesis of Lyme borreliosis.

Introduction

Lyme borreliosis is transmitted by the bite of *Ixodes* ticks infected with *Borrelia burgdorferi* sensu lato (the term “sensu lato” refers to all of the species of Lyme borrelia) [1]. In the United States there is a male predominance of cases [2,3]. This is not necessarily true in Europe where in some countries such as Germany there is a female predominance [4,5]. It has been presumed that the explanation for the unequal gender distribution is that the likelihood of tick exposure is greater for males in the United States and greater for females in certain European countries.

In the United States, only *B. burgdorferi* sensu stricto (the term “sensu stricto” specifically refers to one particular species of Lyme borrelia) causes Lyme borreliosis whereas in Europe the majority of cases of Lyme borreliosis are caused by *B. afzelii* and *B. garinii*, rather than *B. burgdorferi* sensu stricto [1]. Consequently, there are a greater variety of clinical manifestations of Lyme borreliosis in Europe compared with the United States.

In this study we have evaluated the gender distribution according to clinical manifestation among patients with Lyme borreliosis evaluated at the University Medical Center Ljubljana in Ljubljana, Slovenia. Slovenia is a small central European country with 2 million inhabitants. From 2008 to 2011, the annual incidence of Lyme borreliosis was ≈250 cases/100,000 inhabitants [6].

Methods

Patient Population and Serologic Testing Methods

Clinical records were reviewed of patients with Lyme borreliosis aged ≥15 years who were evaluated at the University Medical Center Ljubljana, Ljubljana, Slovenia during 1990-2012. To account for changes in clinic procedures over time, data extraction was limited to periods when information on a specific manifestation was systematically collected, resulting in somewhat different time frames for the different manifestations. Erythema migrans...
patients with Lyme arthritis had objective joint swelling in one or a few large joints, serum IgG antibody to Borrelia antigens and no alternative explanation for the arthritis. The analysis included Lyme arthritis patients diagnosed between 2001 and July 2012. For patients with Lyme arthritis, IgG antibodies to B. burgdorferi sensu lato in serum were determined by an indirect chemiluminescence immunoassay (LIAISON®, Diasorin, Italy) using recombinant VlsE, following the manufacturer’s recommendations.

Patients diagnosed with Lyme neuroborreliosis (LNB) were required to have cerebrospinal fluid (CSF) pleocytosis and at least one of the following: a) concomitant EM, b) isolation of B. burgdorferi sensu lato in serum, or c) evidence of intrathecal synthesis of antibody to Borrelia antigens. Patients diagnosed between October 2005 and July 2012 were included in the analysis. For patients with LNB, antibodies to B. burgdorferi sensu lato in serum and CSF were detected by an indirect chemiluminescence immunoassay (LIAISON®, Diasorin, Italy) using recombinant VlsE, following the manufacturer’s recommendations.

The results of this study conducted at a medical center in Slovenia show that the number of females diagnosed with EM or ACA exceeded the number of males with these cutaneous manifestations of Lyme borreliosis. The opposite was found for non-cutaneous manifestations, where the number of males diagnosed with LNB or Lyme arthritis exceeded the number of females. A male predominance among patients with ACA is quite consistent among case series of ACA reported from other European countries [13–17]. There has also been a female predominance among EM cases in many case series of adult patients from other European countries [17–21], with an especially high proportion of females in patients with recurrent EM in Sweden [22,23]. Similarly, a male predominance for LNB or Lyme arthritis in Europe is by no means unique to Slovenia [4,24–30]. A particular strength of our study is that we had data on a large number of patients with different clinical manifestations of Lyme borreliosis who were diagnosed at a single medical center, thus avoiding confounding variables that may be present when comparisons are made between medical centers.
To our knowledge, this is the first report to document at the same medical center that the proportion of ACA patients who are female is substantially greater than those diagnosed with EM. The difference in the proportion who were females between patients with ACA and EM, however, can be explained almost entirely by differences in the ages of these patients. ACA is a late manifestation of Lyme borreliosis, and patients with ACA were about 15 years older than those with EM. The sex ratio in Slovenia is increasingly biased toward females in older age groups [12], and the difference between ACA and EM patients becomes marginal after controlling for this trend. The observed differences in the proportions of females with EM or ACA, compared with those with either LNB or Lyme arthritis, however, cannot be accounted for by the ages of the patient groups.

Although the patient groups in this study were not from identical time periods, this could only substantively influence the results if there were marked time-related shifts in the sex ratio of the general Slovenian population between 1990 and 2012. Census data, however, indicate that females accounted for 51.5%, 51.1%, and 50.5% of the Slovenian population in 1990, 2000, and 2010 respectively, underscoring that there have been no major shifts in the sex ratio [12]. In addition, if we had limited our analysis of EM cases to the 5,049 cases (48%) occurring during the overlapping years of 2000–2009, the female preponderance was essentially unchanged at 58%. Thus, time-related changes in the sex ratio cannot account for the observed gender differences between cutaneous and non-cutaneous clinical manifestations of Lyme borreliosis.

What might account for the male predominance among patients with LNB and Lyme arthritis? One possibility is that strains of *B. garinii* and *B. burgdorferi* sensu stricto, the Lyme borrelial species thought to be most closely associated with LNB and Lyme arthritis respectively [1], are less likely to infect women than men. This would be plausible if the ticks infected with these species of Lyme borrelia were preferentially found in geographic areas frequented more by men than women, or alternatively, if men were more susceptible to developing infection with these species after being bitten by an infected tick. With either of these scenarios, one might expect, relative to *B. afzelii* infection, that there would be a lower proportion of women with EM who had a positive skin culture for *B. garinii* or for *B. burgdorferi* sensu stricto. Table 2 shows the available Slovenian data on gender for the patients with a positive culture of a skin biopsy sample of an EM skin lesion [31–35]. In support of these hypotheses, a higher percentage of patients with *B. garinii* infection were female compared with those infected with *B. afzelii* (62.2% vs. 53.3%, p = 0.06), and this difference was statistically significant when the rates were adjusted for the age of the patients (59.1% vs. 44.1%, p = 0.003). Indeed, after the age correction there was a male predominance for *B. garinii* infections. However, this pattern was not found for *B. burgdorferi* sensu stricto.

Since LNB and Lyme arthritis presumably arise in most cases through hematogenous dissemination [36], it may be that the likelihood of spirochetemia with highly neurotropic strains of *B. garinii* [37–39], or with strains of *B. burgdorferi* sensu stricto with the strongest propensity to infect joints [37], is greater in males than females. Possible differences between females and males in the immunologic response to borrelia has been discussed by others in trying to explain the much greater likelihood of recurrent episodes of EM in females from Sweden compared with men [21,23]. In the experience at the University Medical Center Ljubljana with patients found to have a positive blood culture for *B. garinii*, there were 12 females compared with 10 males; among patients with a positive blood culture for *B. burgdorferi* sensu stricto, there were 3 females and no males to date. Clearly the available data are too
limited to exclude the possibility that gender might influence the risk of hematogenous dissemination with certain strains of *B. garinii* or *B. burgdorferi* sensu stricto.

Perhaps the explanation is purely behavioral. It could be argued that Slovenian men are simply less likely than Slovenian women to seek health care for EM skin lesions, and thus they become at higher risk for dissemination of Lyme borreliosis to extracutaneous sites. Available data in Slovenia on utilization of health care indicate among individuals aged ≥20 years that women had more outpatient primary care visits in 2010 than men with a ratio of 1.3 visits for women to 1 for men [40]. A counter-argument against this hypothesis, however, is the clear female predominance among patients with ACA, which is also a late manifestation of Lyme borreliosis [1]. However, it may be that men are simply less likely than women in Slovenia to seek medical care for any kind of skin lesion including both EM and ACA.

The potential for biologic significance of gender in infectious diseases is not unique to Lyme borreliosis. For example, it has been previously demonstrated in a murine model of *Borrelia hermsii* infection that males have a significantly higher initial peak level of spirochetemia than females [41]. In another example, it has been observed in patients with *Coxiella burnetii* infection (Q fever) that males have a significantly higher initial peak level of serologic response [42], and experimental studies in mice have confirmed that sex hormones play a role in the pathophysiology of this infection [43].

In conclusion, in this study performed at a single medical center in Slovenia, patients with the cutaneous manifestations of Lyme borreliosis, EM and ACA, were predominantly female, while those with LNB or Lyme arthritis were predominantly men. This pattern of gender distribution has been noted in other [4,15–30], but not all [21,44–47], case series from Europe of these particular clinical manifestations of Lyme borreliosis. Elucidation of the mechanism(s) involved may provide useful insights into the pathogenesis of Lyme borreliosis in Europe.

**Acknowledgments**

The authors would like to thank Lisa Giarratano and Shantale Williams for assistance, Stan Weiss and Joop Schellekens for helpful suggestions, Metka Zaletl from the Institute of Public Health of the Republic of Slovenia for providing information on outpatient visits according to gender, and Brad Biggerstaff, CDC, for statistical assistance.

**Author Contributions**

Conceived and designed the experiments: GPW FS PM KD MVL KO. Analyzed the data: GPW PM KD MVL KO JC ERS DS. Wrote the paper: GPW KD MVL KO FS. Final approval of the version to be published: FS GPW PM KD MVL KO JC ERS DS.

**Table 2.** Correlation between the Species of Lyme Borrelia Isolated from the Skin of Patients with Erythema Migrans and the Gender of Infected Slovenian Patients.

<table>
<thead>
<tr>
<th>Species</th>
<th>Years When Cultured</th>
<th>References</th>
<th>Number of Female Patients with a Positive Culture (%)</th>
<th>Age of Females in Years Median (range)</th>
<th>Number of Male Patients with a Positive Culture (%)</th>
<th>Age of Males in Years Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1993–2007, 2009</td>
<td>35</td>
<td>65 (53.3)</td>
<td>56 (22–79)</td>
<td>57 (46.7)</td>
<td>52 (20–83)</td>
</tr>
<tr>
<td><em>Borrelia burgdorferi sensu stricto</em></td>
<td>1993–2009</td>
<td>Unpublished data</td>
<td>13 (76.5)</td>
<td>55 (33–77)</td>
<td>4 (23.5)</td>
<td>39 (18–47)</td>
</tr>
</tbody>
</table>

doi:10.1371/journal.pone.0064110.t002

References

4. Fulop B, Poggensee G (2008) Epidemiological situation of Lyme borreliosis, EM and ACA, were predominantly female, while those with LNB or Lyme arthritis were predominantly men. This pattern of gender distribution has been noted in other [4,15–30], but not all [21,44–47], case series from Europe of these particular clinical manifestations of Lyme borreliosis. Elucidation of the mechanism(s) involved may provide useful insights into the pathogenesis of Lyme borreliosis in Europe.


