Epidemiology of Lyme disease

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SUMMARY

Lyme borreliosis (LB) is the most common tick-borne disease in Europe and North America. LB occurs in all age groups, with equal prevalence in men and women. In Croatia the spirochete *Borrelia burgdorferi* (Bb) was first isolated in 1991 at the Department of Dermatology and Venereology, Zagreb University Hospital Center from the skin of a patient with Erythema chronicum migrans (ECM) and was designated as P_1 Zagreb. In Croatia ECM as an early skin manifestation of LB was first described by Forenbacher in 1940, followed by Mohar in 1982, Maretić et al. in 1989, Curl 1991, Kansky 1992, Bolanča-Bumber 1997. Šitum described in 1998 in Croatia clinical and laboratory analysis in a group of 148 selected subjects (20 from a risk population of forestry workers from a non-endemic area, 82 from a risk population of forestry workers from a LB endemic area, and 46 LB affected subjects).

In 130 out of 148 subjects with positive tick bite history, clinical manifestation of LB were present in 49 and absent in 81 subjects. Sixty out of 148 study group subjects had a positive IFA test, and 24 had positive PCR test.

The LB is very important for dermatovenerologists because of skin manifestations: ECM, lymphadenosis benigna cutis (LBC) and acrodermatitis chronica atrophicans (ACA).

The appropriate treatment of ECM as early as possible is of utmost importance to prevent the possible occurrence of late manifestations of LB (neurological cardiologic and rheumatologic sequelae). Endemic LB areas in Croatia are Central and North Croatia.

KEY WORDS

Lyme disease, borreliosis, epidemiology, Croatia

Introduction

Lyme borreliosis (LB) or Lyme disease currently is the most common tick-borne disease in Europe and North America. LB is a multisystem disease caused by the spirochete *Borrelia burgdorferi* (Bb). Small rodents, hedgehog, birds, deer and vole are natural Bb reservoirs, whereas domestic animals (cattle, sheep, dog, etc.) play an important role in the spread of the disease in inhabited areas (1,2). LB is usually transmitted by ticks

Table 1. Frequency of early manifestation of Lyme disease at Dermatology and Venereology Health Care Services in Central, North and East Croatia (1985-1994)

Dermatologic Service	ECM	Tick bites
Koprivnica	131	25
Karlovac	171	66
Čakovec (1991-1994)*	98	-
Slavonski Brod (1993-1994)	13	6
Ogulin	112	43
Sisak	101	74
Osijek	216	-
TOTAL	848	214

In Croatia from 1988 till 1990 in same regions were recorded 907 cases of ECM

**Data obtained from the Polyclinic for Infectious Diseases (1991-1994) and Dermatovenerology Service until 1994*

from the family Ixodidae (3). The first description of a patient with LB is attributed to Buchwald, a German, as early as 1883 (4, 5), whereas the association between tick bite and skin changes was first observed by Afzelius, a Swede, in 1909, and Lipschutz, an Austrian, in 1913 (6), who called it erythema chronicum migrans (ECM) (7). In 1920, Garini and Bujadoux reported on a patient in whom ECM-like purpura developed at the site of tick bite (8), and in 1930 Helstrom described a patient with erythema, fever and meningitis secondary to tick bite (9). In Croatia, ECM, i.e. skin manifestation of LB, was first described by Forenbacher in 1940 (10), followed by Mohar in 1982 (11).

In 1972, an increasing number of patients with arthritis was recorded in the Lyme district, Connecticut, USA; in 1975, 39 children were affected with juvenile rheumatoid arthritis in the districts of Old Lyme, Lyme and East Haddam, Connecticut. Careful epidemiologic and clinical studies revealed the disease to be due to a tick-borne infection, caused by a penicillin sensitive agent. The disease was named Lyme arthritis (12).

Table 2. Lyme borreliosis: frequency of infections in the period 1992-1998 (54)

LYME BORRELIOSIS: Frequency of infections in the period 1992-1998	
Year	Patients
1992	93
1993	315
1994	255
1995	268
1996	335
1997	229
1998	248

Population in Croatia - 4.501.149

In 1982, Burgdorfer and coworkers from USA identified and isolated the spirochete from the intestine of the *Ixodes dammini* tick (2,13). A year later, in 1983, the spirochete was also isolated in Europe from the *Ixodes ricinus* tick (14). Based on DNA morphology and guanine and cytosine content, according to the classification of Barbour and coworkers (15), the etiologic agent LB belongs to the family *Spirochaetaceae, genus Borrelia, species Borrelia burgdorferi.* Bb is a gram-negative microaerophilic bacterium.

In Croatia, Bb was first isolated in 1991 at the Department of Dermatology and Venereology, Zagreb University Hospital Center, from the skin of a patient with ECM, and was designated as P1 Zagreb (16 a,b). Electrophoretic analysis of the Bb protein content revealed six major proteins of different molecular mass (OspA, OspB, OspC, p41, p60 and p100).

Various tick species from the *genus Ixodes* (hard ticks) of the large family Ixodidae, i.e. *Ixodes ricinus* in Europe and *Ixodes persulcatus* in Eurasia transmitting *B. afzelii*, the cause of early and late skin manifestations of LB, and *B. garinii* generally causing EM and neuroborreliosis, are the main vector in Bb transmission (17). *Ixodes ricinus* occasionally serves as a vector for *B. valaisiana* (group VS116) and *B. lusitaniae* (group PotiB2), which do not cause an overt clinical picture of LB (18). *Ixodes persulcatus* has also been found in Japan, transmitting *B. valaisiana* (19). In northeast USA, *Ixodes dammini* and *Ixodes scapularis* usually transmit Bb, which mostly causes early and late skin manifestation of LB, arthritis and neuroborreliosis (20, 21). In the western part of the USA, *Ixodes pacificus* and *Ixodes neotomae* (22) serve as vectors for the Borrelia species DN127 and CA55, which have not yet been associated with any clinical symptoms of LB. *Ixodes dentatus*, which transmits *B. andersoni*, a new genomic group of Bb 21038 (23) as yet showing no overt symptoms of LB (24), has also been recorded in America. *Ixodes uriae*, mostly serving as a vector for *B. garinii*, has been found on the northern and southern hemisphere (25), whereas *Ixodes ovatus*, a vector for non-pathogenic *B. japonica*, is most common in Japan (26).

Ixodes cholocyclus (27), *Amblyomma americanum* (28) and *Dermacentor variabilis* as representatives of

other tick species in highly endemic areas of north-east America are highly infected (29). *Ixodes trianguliceps* and *Ixodes acuminatus* have been reported in northern France as Bb vectors (30). Other possible vectors include some mosquito and fly species (31). Tick infectivity with Bb varies in different geographic regions. So, in the north-east, highly endemic area of USA, the percentage of infected *Ixodes dammini* and *Ixodes scapularis* ticks is 10% - 50% (32), whereas on the west coast with sporadic occurrence of LB the percentage of infected *Ixodes pacificus* ticks is 1% - 3% (33). In Europe, the infection rate of *Ixodes ricinus* ticks ranges from 3% to 45% (4.5% - 30.8% in Germany and Switzerland (33, 34), and 23.5% in Slovenia (35)). According to Golubić, 45% of Bb infected ticks are found in northwest Croatia (18). In the USA, white-leg mice are the main reservoir of *Ixodes scapularis* (36, 37). In Europe, major reservoirs of Borrelia are small rodents, wood mice, field mice, yellow-neck mice, voles and dormouses (38). Birds, deer, doe, boar, rabbit (39) and numerous domestic animals such as dog, horse, cattle, etc. are also significant reservoirs of Bb. (40-43). All the three tick species can parasitize on man. Transovarial transmission of Bb has also been reported (44); however, inherited infection naturally occurs in less than 1% of ticks (45). The life cycle of Bb depends on the transstage transmission: from infected nymph to host in early summer, and from infected host to larva in late summer. The latter will subsequently become an infected nymph to repeat the cycle in the year to come (46). Bb is mostly found in the tick mid-intestine, however, their systemic presence has also been reported (38). During the attachment period, spirochetes were found in the saliva 2-4 days after contact with the host (47), probably being transmitted by saliva from the salivary glands during tick feeding or with gastric content vomit. It has been experimentally demonstrated that tick has to parasitize on the host for at least 24 hours or more to allow for spirochete transmission (48). The survival of Bb in a mosquito is limited to 6 days (49). The intestine is considered to be an optimal environment for the growth of Bb, due to the short lifespan of enterocytes during the tick life cycle (50). The use of ticks as vectors for Bb also has other advantages such as prolonged exposure on a host with low pathogen content, and simultaneous intake of the pathogenic agent interfering with the host's inflammatory response, e.g., anticoagulants and platelet aggregation inhibitors (51, 52).

In the northwest Croatia, an endemic area for Lyme borreliosis, four genomic *B. burgdorferi* sensu lato groups were identified in the *Ixodes ricinus* ticks: *B. afzelii, B. garnii, B. valaisiana* (group VSS116), and *B. burgdorferi* sensu stricto (1)

Šitum in her study comprised specific endemic areas of Lyme disease in Croatia and results confirmed that *B. afzelii* is the main causative agent of ECM in the studied group from that area.(1)

As similar studies have not been made in other parts of Croatia, there is a dilemma whether *B. afzelii* is the causative agent of the most frequent manifestation of the Lyme disease – ECM in other parts of Croatia. (1)

It is necessary to investigate other clinical types of Lyme disease such as Lyme arthritis and neuroborreliosis in order to determine whether other Bb genospecies are also included in the etiology of extracutaneous types of Lyme disease.

Over the last ten years, the Lyme disease (LD) has grown into a public health problem, especially in USA and central Europe. Additionally to the skin, joints, heart and central nervous system can be involved.

LB occurs in all age groups, with equal prevalence in men and women. The Lyme disease is very important for dermatologists because of the three described diseases: ECM, LBC and ACA.

From 1988 till 1990 in Central and North Croatia, which are endemic LB areas, 907 cases of ECM were found (53). There were 216 cases of ECM in Osijek (East Croatia) in 1995. Table 1. The data on LB frequency during 1992-1998 period in Croatia are shown in Table 2 (54).

Conclusion

In Croatia are geographic and climatic characteristics favorable for the life cycle and spread of the ticks of the Ixodes. (i.e. woodland with humid climate). Endemic areas for LB in Croatia are: Central, North and East parts.

Dermatovenereologists and infectologists perform diagnosis of LB in Croatia. Laboratory diagnosis of antibodies to Bb using indirect immunofluorescence (IF) since 1988 and Bb cultivation since 1991 in Department of Dermatology and Venereology Zagreb University School of Medicine, in Zagreb. ELISA assay is performing in Department for Infectious Diseases Zagreb.

An appropriate treatment of ECM is important in prevention of possible occurrence of late LB manifestation. Proper education of general practitioners and close collaboration with dermatovenerologists is necessary for health care and prevention in endemic areas.

REFERENCES

1. Šitum M. Dijagnostika Lajmske bolesti pomoću lančaste polimerazne reakcije istraživanja u Hrvatskoj. University School of Medicine. Doctoral dissertation, 1998: 153.

2. Curl A. Bolesti prenesene i izazvane ubodom krpelja. Acta Derm Iug 1991; 18: 123-9.

3. Anderson JF. Epizooetiology of Lyme borreliosis. Scand J Infect Dis 1991; 77: 23-4.

4. Buchwald A. Ein Fall von Diffuser Idiopathischer Haut Atrophie. Arch Derm Syph 1883; 15: 553-6.

5. Herxeimer K, Hartman K. Uber Acrodermatitis Chronica Atrophicans. Acta Dermatol 1902; 61: 57-76.

6. Afzelius A. Verhandlungen der Dermatologischen Gesellschaft zu Stockholm. Arch Dermatol Syph 1910; 101-404.

7. Lipschutz B. Uber eine Seltene Erythemaform (Erythema chronicum migrans). Arch Dermatol Syph 1914; 118: 349-56.

8. Garini C, Bujadoux C. Paralysis par estiques. J Med Lyon 1922; 71: 765-7.

9. Hellstrom S. Erythema chronicum migrans Afzelius. Acta Derm Venereol (Stockh) 1930; 1: 315-21.

10. Forenbacher G. Erythema chronicum migrans Lipschutz. Zbl Haut Geschlechtskrankheit 1940; 64: 273-5.

11. Mohar N.: Erythema chronicum migrans. Clinical and epidemiological observations on Rijeka district. Acta Derm Jug 1982; 9: 155-8.

12. Steere AC, Malawista SE, Snydman DR, et al. Lyme arthritis: an epidemic of oligoarthritis in children and adults in three Connecticut communities. Arthritis Rheum, 1977; 20: 7-17.

13. Burgdorfer W, Barbour AG, Hayes SF, Banach JL, Grunwald E, Davis JP. Lyme disease – a tick borne spirochetosis? Science 1982; 216: 1317-9.

14. Asbrink E, Hovmark A, Hederstedt B. The spirochetal etiology of ACA Herxheimer. Acta Derm Venereol Stockh 1984; 64: 506-12.

15. Barbour AG. Isolation and cultivation of Lyme Disease spirochetes. Yale J Biol Med 1984; 57: 521-5.

16a. Bolanča-Bumber S. Uloga borelije burgdorferi u etiopatogenezi kožnih manifestacija Lyme bolesti. Zagreb, Hrvatska: Medicinski fakultet Sveučilišta u Zagrebu, 1992; 78 str. Disertacija.

16b. Bolanča-Bumber S, Šitum M, Balić-Winter A, Skerlev M, Lipozenčić J, Dobrić I, Marinović B, Presečki V, Baričević B, Basta-Juzbašić A. First isolation of Borrelia burgdorferi sensu lato in Croatia. Acta Dermatovenerolog Croat 1997;5(3):95-9.

17. Krampitz HE. In vivo isolatio and maintenence of some wild strains of European hard tick spirochetes in mammalian and arthropod hosts: a parasitologist's view. Zbl Bakt Hyg A 1986; 263: 21-6.

18. Golubić D. Epidemiološke, ekološke i kliničke karakteristike Lyme borelioze u sjeverozapadnoj Hrvatskoj. Zagreb, Hrvatska: Medicinski fakultet Sveučilišta u Zagrebu, 1997; 130 str. Disertacija.

19. Takada N, Ishiguro F, Iida H, et al. Prevalence of Lyme borrelia in tick especially Ixodes persulcatus (Acari: Ixodidae) in central and western Japan. J Med Entomol 1994; 31: 474-8.

20. Steere AC, Malawista SE. Cases of Lyme disease in the United States: locations correlated with distributions of Ixodes dammini. Ann Intern Med 1979; 91: 730-3.

21. Oliver JH, Owsly MR, Hutcheson HJ, et al. Conspecificity of the ticks Ixodes scapularis and Ixodes dammini (Acari: Ixodidae). J Med Entomol 1993; 30: 54-63.

22. Lane RS, Burgdorfer W. Transovarial transstadial passage of Borrelia burgdorferi in the westernlegged tick Ixodes pacificus (Acari: Ixodidae). Am J Trop Med Hyg 1987; 37: 188-92.

23. Marconi RT, Liveris D, Schwartz I. Identification of novel insertion elements, restriction fragment length polymorphism patterns, a discontinuous 23s rRNA in Lyme disease spirochetes (Phylogenetic analyses of rRNA gene and their intergenic spacers in Borrelia japonica sp. nov. and genomic group 21038 (Borrelia andersonii sp. nov.) isolates. J Clin Microbiol 1995; 33: 2427-34.

24. Anderson JF, Magnarelli LA, LeFebvre RB, et al. Antigenically variable B. Burgdorferi isolated from cottontail rabbits and Ixodes dentatus in rural and urban areas. J Clin Microbiol 1989; 27: 13-20.

25. Olsen B, Jaenson TGT, Noppa L, et al. A Lyme Borreliosis cycle in seabirds and Ixodes uriae tick. Nature 1993; 362: 340-2.

26. Kawabata H, Masuzawa T, Yanagihara Y. Genomic analysis of Borrelia japonica sp. nov. isolated from Ixodes ovatus in Japan. Microbiol Immun 1993; 37: 843-9.

27. Piesman J, Stone BF. Vector competence of the Australian paralysis tick, Ixodes holocyclus, for the Lyme disease spirochete, Borrelia burgdorferi. Intern J Parasitol 1991; 21: 109-11.

28. Schulze TL, Bowen GS, Bosler EM, Lakat MF, Parkin WE, Altman R, Ormiston BG, Shisler JK. Amblyomma americanum: a potential vector of Lyme disease in New Jersey. Science 1984; 224: 601-3.

29. Falco RC, Fish D. Tick parasitizing humans in a Lyme disease endemic area of southern New York state. Am J Epidemiol 1988; 128: 1146-52.

30. Magnarelli LA, Anderson JF, Barbour AG. The etiological agent of Lyme disease in deer flies, horse flies and mosquitoes, J Infect Dis 1986; 154: 355-8.

31. Burgdorfer W, Hayes SF, Benach JL. Development of Borrelia burgdorferi in Ixodes tick vectors. Ann NY Acad Sci 1988; 539: 172-9.

32. Burgdorfer W, Lane RS, Barbour AG, Gresbrink RA, Anderson RJ. The western black-legged tick, Ixodes pacificus: a vector of Borrelia burgdorferi. Am J Trop Med Hyg 1985; 34: 925-30.

33. Stanek G, Pletschette M, Flamm H, et al. European Lyme borreliosis. Ann NY Acad Sci 1988; 539: 274-82.

34. Hulsse C, Herrmann, H, Oheim S, Schroder LW, Stenglin M. Investigations on the Dissemination of Borrelia burgdorferi in the State of Mecklenburg-Western Pomerania. Hyg Med 1995; 20: 345-50.

35. Ružić-Sabljić E, Strle F, Cimperman J. The Ixodes ricinus as a vector of Borrelia burgdorferi in Slovenia. Eur J Epidemiol 1993; 9: 396-400.

36. Donahue JG, Piesman J, Speilman A. Reservoir competence of white-footed mice for Lyme disease spirochetes. Am J Trop Med Hyg 1987; 36: 92-6.

37. Levin JF, Wilson ML, Spielman A Mice as reservoir of the Lyme disease spirochete. Am J Trop Med Hyg 1985; 34: 355-60.

38. Anderson JF, Johnson Rc, Magnarelli LA, Hyde FW. Involvement of birds in the epidemiology of the Lyme disease agent Borrelia burgdorferi. Infect Immun 1986; 51: 394-6.

39. Lane RS, Burgdorfer W. Potential role of native and exotic deer and their associated ticks (Acari: Ixodidae) in the ecology of Lyme disease in California, USA. Zbl Bakt Hyg A 1986; 263: 55-64.

40. Bosler EM, Camay H, Ormiston BG, Benach JL. Spirochete-associated arthritis (Lyme disease) in a dog. JAVMA 1984; 185: 219-20.

41. Burgess EC, Mattison M. Encephalitis associated with Borrelia burgdorferi in a horse. JAVMA 1987; 191: 1457-8.

42. Burgess EC, Gillette D, Picket JP. Arthritis and panuveitis as manifestation of Borrelia burgdorferi infection in a Wisconsin pony. JAVMA 1986; 189: 1340-2.

43. Burgess EC. Borrelia burgdorferi infection in Wisconsin horses and cows. Ann NY Acad Sci 1988; 539: 235-43.

44. Burgdorfer W, Barbour AG, Hayes SF, Peter O, Aeschliman A. Erythema chronicum migrans – a tickborne spirochetosis. Acta Trop 1983; 40: 79-83.

45. Plesman J, Donahue JG, Mather TN, Spielman A. Transovarially acquired Lyme disease spirocheres (Borrelia burgdorferi) in field-collected larval Ixodes dammini (Acari: Ixodidae). J Med Entomol 1986; 23: 291.

46. Matuscha FR, Spielman A. The emergency of Lyme disease in changing environment in North America and central Europe. Exp Appl Acarol 1986; 2: 337-53.

47. Ribeiro JMC, Mather TN, Piesman J, Spielman A. Dissemination and salivary delivery of Lyme disease spirochetes in vector ticks (Acari: Ixodidae). J Med Entomol 1987; 24: 201-5.

48. Piesman J, Mather TN, Sinsky RJ, Spielman A. Duration of ticks attachment and Borrelia burgdorferi transmission. J Clin Microbiol 1987; 25: 557-8.

49. Magnarelli LA, Freier JE, Anderson JF. Experimental infections of mosquitoes with Borrelia burgdorferi, the endemic agent of Lyme disease. J Infect Dis 1987; 156: 694-5.

50. Korenberg EI. Problems of epizootiology, epidemiology and evolution associated with modern Borrelia taxonomy, 17-47, in U: Yanagihari Y, Masuzawa T. ur.: Present status of Lyme disease and biology of Lyme Borrelia. 1994. Proct Int Symposium Lyme Disease Japan. Kanzanji, Hamamatsu, Shizuoka, Japan.

51. Randolph SE, Nuttal PA. Nearly right or precisely wrong? Natural versus laboratory studies of vector - borne disease. Parasitol Today 1994; 10: 458-62.

52. Ribeiro JMC, Makaoul GT, Levine J, Robinson DR, Spielman A. Anthemostatic anti-inflammatory and immunosuppressive properties of the saliva of a tick Ixodes dammini. J Exp Med 1985; 161: 332-4.

53. Kansky A. Lyme disease is spreading to the south-east (Skin manifestation in Croatia 1988-1990). Acta Dermatovenerologica APA 1992; 3: 93-5.

54. Croatian Health Statistic Yearbook 1988. Lyme borreliosis: frequency of infections in the period 1992-1998. Croatian Institute for Health, Zagreb, 1999.

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