Jpn. J. Infect. Dis., 68, 1–4, 2015

Original Article

Epidemiological Features and Clinical Manifestations of Lyme Borreliosis in Korea during the Period 2005–2012

Shinje Moon[1†], Yeongseon Hong[2†], Kyu-Jam Hwang[3], Suyeon Kim[3], Jihye Eom[3], Donghyok Kwon[3], Ji-Hyuk Park[4], Seung-Ki Youn[1], and Aeree Sohn[5*]

[1]*Division of Epidemic Intelligence Service, Korea Centers for Disease Control and Prevention, Chungcheongbuk-do;*
[3]*Division of Zoonoses, Korea National Institute of Health, Chungcheongbuk-do;*
[2]*Department of Public Health, Sahmyook University Graduate School, Seoul;*
[5]*Department of Health Management, Sahmyook University, Seoul; and*
[4]*Department of Preventive Medicine, Dongguk University College of Medicine, Gyeongsangbuk-do, Korea*

SUMMARY: Lyme borreliosis is one of the most common tick-borne infections in the northern hemisphere. However, the epidemiological features and clinical manifestations of this disease in Korea are unknown. The present study is the first to investigate the characteristics of Lyme borreliosis in Korea. We traced suspected cases of Lyme borreliosis during the period 2005–2012. Of the 16 identified patients with the disease, 11 had acquired autochthonous infection within Korea, while 5 patients were infected outside Korea. The history of past exposure was investigated in 8 of the 11 patients with autochthonous infection; 5 of these 8 patients (62.5%) were suspected to have acquired the infection in the northeastern alpine region. Clinically, of 11 patients with autochthonous infection, 6 (54.5%) showed early skin manifestations, 4 (36.4%) showed neurological manifestations, and 1 (9.1%) showed acrodermatitis chronica atrophicans. In conclusion, Lyme borreliosis could be endemic in the northeastern alpine region of Korea, and neurological and early skin manifestations are likely to be the major clinical characteristics of autochthonous Lyme borreliosis in Korea.

INTRODUCTION

Lyme borreliosis is one of the most common tick-borne infections in the northern hemisphere, with more than 20,000 patients infected with Lyme borreliosis being reported in the United States each year (1). In Europe, the disease has been reported in forested areas, particularly in Sweden, Germany, Austria, and Slovenia (2). The disease has also been widely reported in Asian countries such as China (3,4) and Japan (5,6). Although several cases of Lyme borreliosis have been reported in Korea (7–10), information on the overall epidemiological characteristics and clinical manifestations of the disease in Korea is not available. The identification of these characteristics would provide further epidemiological and clinical information on Lyme borreliosis in eastern Asia. Furthermore, this information is essential for formulating more efficient national policies for the prevention of Lyme borreliosis in Korea. The present study aims to identify the epidemiological characteristics and clinical manifestations of Lyme borreliosis in Korea by tracing and investigating patients with the disease during the period 2005–2012.

Received December 19, 2013. Accepted April 4, 2014.
J-STAGE Advance Publication November 25, 2014.
DOI: 10.7883/yoken.JJID.2013.462
*Corresponding author: Mailing address: Dept. of Health Management, Sahmyook University, 26-21 Kongneung-Dong, Nowon-Ku, Seoul, Korea. Tel: +82-2-3399-1630, Fax: +82-2-3399-1639, E-mail: aeree@syu.ac.kr
†These authors contributed equally to this work.

MATERIALS AND METHODS

Study setting: Lyme borreliosis was designated a national notifiable infectious disease in Korea on December 30, 2010, and a national surveillance system was established (11). Since 2011, a total of 14 suspected patients have been reported to this national surveillance system. We conducted epidemiological investigations of these suspected patients. However, information on Lyme borreliosis prior to the implementation of the national surveillance system is not available. To identify patients before 2011, we used diagnostic data from the Division of Zoonoses, Korea National Institute of Health (KNIH), which is the only laboratory in Korea that performs indirect immunofluorescent antibody (IFA) and immunoblot assays for *Borrelia burgdorferi* sensu lato (*B. burgdorferi* sl). This database included data from a previous serological study on Lyme borreliosis (12). A total of 2,395 serum specimens were examined, and 57 suspected patients showed positive results in IFA and immunoblot assays during the period 2005–2010. We traced and conducted epidemiological investigations of the suspected patients who had positive results from this laboratory. Epidemiological investigations were conducted and included interviews with patients and retrospective examination of medical records from 23 hospitals where patients had undergone treatment. The following variables were collected for each patient: demographic features such as gender, age, residential address, and occupation, history of travel within 6 months from the date of disease onset, history of tick bites, clinical manifestations, and laboratory findings.

Laboratory investigations: The bacterial strains *B.*

burgdorferi sensu stricto B31, *B. afzeli* pKo, and *B. garinii* 935T were cultured in Barbour-Stoenner-Kelly (BSK)-II medium (Sigma, St. Louis, MO, USA) at 34°C and utilized for preparation of slides for IFA assay. The test serum was subjected to 2-fold serial dilutions from 1:16 to 1:1,024. Samples with titers of 1:16 for IgM or 1:256 for IgG were defined as positive. Samples that showed positive results in IFA assay were subsequently subjected to immunoblot assay.

Immunoblot assays were conducted during the period 2005–2009 using the recom-Blot *Borrelia* immunoblot test (Mikrogen, Neuried, Germany). The test serum was diluted with the reactant solution at a ratio of 1:200 and 1:100 for IgG and IgM, respectively. The recom-Blot *Borrelia* immunoblot test detects IgG and IgM antibodies with specificity for *B. burgdorferi* using recombinant antigens of *B. burgdorferi* sl, such as p100, VlsE, p39, OspA, OspC, p41, and p18. Scores were calculated according to the presence and level of antibodies for each antigen. Scores of ≤ 4 were defined as negative, 5–6 as borderline, and ≥ 7 points as positive (12). From 2010 onwards, the immunoblot kit recomLine *Borrelia* IgG/IgM (Mikrogen) was employed. The test serum was diluted with the reactant solution at a ratio of 1:100 and 1:50 for IgG and IgM, respectively. Calculated scores of ≤ 5 were defined as negative, score 6 as borderline, and > 6 as positive.

Case definition: Patients with Lyme borreliosis were defined as having clinical manifestations and laboratory confirmation of the disease (KCDC, 2011). The clinical manifestations include the following: i) erythema migrans (EM); ii) atypical erythematous lesion along with a history of tick bites; iii) acrodermatitis chronica atrophicans (ACA); iv) neurological manifestations, including cranial neuritis, radiculoneuropathy, meningitis, or encephalomyelitis; v) musculoskeletal manifestations, including arthritis; vi) cardiovascular manifestations, including acute onset of high-grade atrioventricular conduction defect (13,14).

The laboratory criteria included the isolation of *B. burgdorferi* or positive results in IFA and immunoblot assays. Patients who failed to present with any clinical manifestations (as defined above) or who were diagnosed with other infectious or autoimmune diseases were excluded from the present study.

Ethics statement: This study was approved by the Institutional Review Board of KNIH (IRB No. 2013-08EXP-01-P). Informed consent was waived by the board.

RESULTS

Epidemiological investigations resulted in the identification of a total of 16 patients with Lyme borreliosis. Eleven of these patients had acquired autochthonous infection within Korea: 1 in 2005, 2 in 2007, 3 in 2008, 3 in 2009, and 2 in 2012 (11). The remaining 5 patients were infected outside Korea.

(i) Autochthonous Lyme borreliosis in Korea: **(i-i) Demographic features**: The mean age of patients was 41.9 years, ranging from 33 to 53 years. Five patients (45.4%) were in their 30s, 4 (36.4%) in their 40s, and 2 (18.2%), in their 50s. Six patients (54.5%) were male. The majority of patients (6, 54.5%) resided in the Seoul metropolitan region, followed by the northeastern (3, 27.3%), southeastern (1, 9.1%), and mid-western (1, 9.1%) regions. The occupations of 9 patients were identified, and those of 7 patients were not associated with outdoor work (Table 1). **(i-ii) Epidemiological features**: The history of past exposure was investigated in 8 of 11 patients; 5 patients (62.5%) were suspected to have acquired the infection in the northeastern alpine region, and 1 patient each in the northwestern, mid-western, and southeastern regions (Figure 1). **(i-iii) Clinical manifestations**: The clinical manifestations were investigated in 11 patients; 5 patients (45.4%) showed the presence of EM, 1 patient (9.1%) had an atypical erythematous lesion with a history of tick bites, another patient (9.1%) had ACA, and 4 patients (36.6%) exhibited neurological abnormalities (Table 1). Ten of 11 patients were subjected to follow-up: 8 patients showed complete recovery, 1 patient had persistent ar-

Table 1. Demographic and clinical features of patients with autochthonous Lyme borreliosis in Korea during period 2005–2012

Patient	Age	Gender	Occupation	Tick-bite	Incubation period	Clinical manifestation	IgG	IgM	Western blot
Patient 1*	46	F	Householder	Positive	10 days	Erythema migrans with fever, headache, myalgia and fatigue	1:256	<1:16	Positive
Patient 2*	44	M	Office worker	Positive	1 month	Erythema migrans with myalgia and arthralgia	1:516	<1:16	Positive
Patient 3	48	F	Householder	Positive	5 days	Multiple atypical erythematous lesions with fever, myalgia and fatigue	1:128	1:16	Positive
Patient 4	38	M	Office worker	Unknown	3 months	Neurologic manifestations (gait disturbance, bilateral ptosis)	1:128	1:16	Positive
Patient 5	53	F	Unknown	Unknown	Unknown	Neurologic manifestation (facial palsy)	1:256	<1:16	Positive
Patient 6	34	F	Householder	Unknown	4 months	Acrodermatitis chronica atrophicans	1:128	1:16	Positive
Patient 7	34	M	Unknown	Unknown	Unknown	Neurologic manifestations (gait disturbance, seizure)	1:512	<1:16	Positive
Patient 8	50	F	Botanist	Positive	3 weeks	Erythema migrans with fever, headache and myalgia	1:512	<1:16	Positive
Patient 9	33	M	Office worker	Positive	2 weeks	Erythema migrans with myalgia	1:32	<1:16	Positive
Patient 10	37	M	Office worker	Unknown	Unknown	Neurologic manifestation (facial palsy)	1:256	<1:16	Positive
Patient 11	44	M	Soldier	Unknown	Unknown	Erythema migrans	1:64	1:32	Positive

*: Data from Moon et al. Osong Public Health Res Perspect. 2013; 4: 52–6 (ref. 11).

thralgia, and another patient had neurological sequelae.
(i-iv) Clinical laboratory findings: Clinical laboratory test results were available for 8 patients. The mean white blood cell (WBC) count was 8,855/mm^3, and 2 patients developed leukocytosis with WBC counts of 13,500/mm^3 and 11,300/mm^3, respectively. The hemoglobin and platelet counts were within normal limits at baseline in every patient (mean hemoglobin = 14.4 g/dL, mean platelet count = 260,000/mm^3). The mean levels of serum AST and ALT were 23.3 u/L and 20.6 u/L, respectively, with 1 patient showing elevated AST (40 u/L). The CRP level was examined in only 6 patients and was found to be elevated (37.9 mg/L) in 1 patient.
(ii) Lyme borreliosis infection outside Korea: Five patients were infected outside Korea. The clinical manifestations included EM in 4 patients and atypical erythematous lesion with a history of tick bites in 1 patient. None of these patients exhibited any neurological manifestations, and all of them showed complete recovery (Table 2).

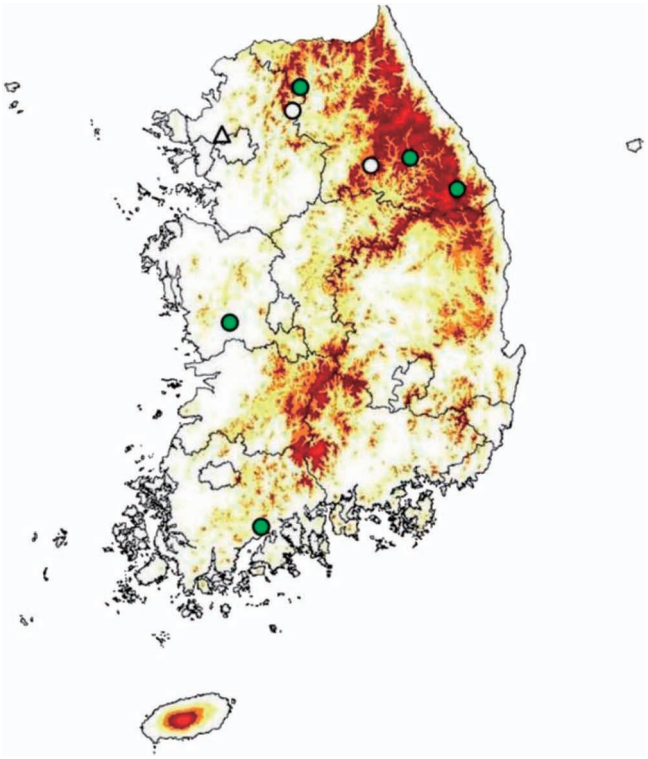

Fig. 1. (Color online) Regions where patients may have experienced tick bites. ○: Location the patients visited for outdoor activity. △: Location where patients with no history of travel lived. Green circles: Location where patients had confirmed tick bites.

DISCUSSION

Since the first reported case of Lyme borreliosis in Korea in 1993 (7), there were reports of 4 additional sporadic cases until 2005 (8–10). From the succeeding year, reports of patients with Lyme borreliosis could be continuously monitored and were investigated in the present study. These reports suggest the occurrence of endemic areas of Lyme borreliosis in Korea. Several studies on the seroprevalence of *B. burgdorferi* sl suggest that the northeastern region is likely to be an endemic area of Lyme borreliosis (15,16); however, systematic study on the epidemiology or spread of the disease in the country has not been performed to date. The results of the present study are significant from the perspective of elucidating the epidemiology of Lyme borreliosis in Korea. The reason for the frequent infection of patients in the northeast region is unclear; however, studies conducted in China and Japan (3–6) suggest that the distribution of *Ixodes persulcatus*, the taiga tick, could play a role in this phenomenon. Accordingly, this tick has been detected mainly in the northeastern alpine region of Korea, where the cool climatic conditions provide a suitable habitat for this vector (17–20).

Diverse clinical manifestations of Lyme borreliosis have been observed in different regions (1,2,21,22). The present study conducted in Korea reported a higher frequency of the neurological manifestations in comparison with that in the United States and Europe. Although 3 of 4 patients with neurological manifestations failed to recall the exposure date and exhibited low IgM titer, their clinical symptoms were characteristic of early as opposed to late neurological manifestations. Therefore, early neurological manifestations could be considered the major clinical characteristic of autochthonous Lyme borreliosis in Korea. In contrast, all patients infected outside Korea during the same period showed skin manifestations but no neurological symptoms. However, given the small sample size of the present study, further studies are required to accurately determine the clinical characteristics of Lyme borreliosis in Korea.

Laboratory tests revealed that the WBC count, hemoglobin concentration, and platelet count in patients with Lyme borreliosis were typically within the normal range. A previous study, however, showed that about 35% of patients in the United States and up to 20% of patients in Europe exhibited slightly elevated liver function, in particular, AST and ALT levels (22).

Table 2. General and clinical characteristics of patients infected outside Korea

Patient	Age	Gender	Visit	Tick-bite	Clinical manifestation	IgG	IgM	Western blot
Patient A	46	F	France	Positive	Erythema migrans	1:256	<1:16	Positive
Patient B	66	F	Unknown	Positive	Erythema migrans	1:256	1:256	Positive
Patient C	39	F	USA	Positive	Multiple atypical erythematous lesions	1:256	1:32	Positive
Patient D	64	F	USA	Positive	Atypical erythematous lesions	1:256	<1:16	Positive
Patient E	64	F	Canada	Unknown	Erythema migrans	Unknown*	Unknown*	Unknown*

*: Laboratory tests were conducted outside Korea.

A similar pattern was revealed in the present study.

The present study is significant because it is the first to describe the epidemiological features and clinical manifestations of autochthonous Lyme borreliosis in Korea. However, we acknowledge its potential limitations. First, the sample size is small due to lower number of patients; therefore, conclusions with respect to the epidemiological features and clinical manifestations could be biased. Second, patients with early and localized infection are likely to be unrepresented, because they are more easily overlooked than patients with disseminated or late infection. Third, diagnosis was based on serological examination alone, and cerebrospinal fluid samples were not examined for neuroborreliosis.

In conclusion, Lyme borreliosis occurred with the highest frequency in the northeastern region of Korea. Neurological and early skin manifestations were among the major clinical characteristics of the disease, as observed in the present study. However, conducting extended inspections for tick distribution, continuous surveillance for Lyme borreliosis, and the isolation of causative pathogens from ticks and humans are essential for clearly elucidating the epidemiological features and clinical characteristics of the disease.

Acknowledgments We express our gratitude to colleagues in the Division of Epidemic Intelligence Service in KCDC and in the Division of Zoonoses in KNIH for their help and co-operation in this project. This study was supported by grants from the Korea Centers for Disease Control and Prevention (No. 4800–4838–300 and No. 4800–4837–301). The authors wish to acknowledge the support for this project from the Sahmyook University Research Fund.

Conflict of interest None to declare.

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