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Original Article

Case control study: Serological evidence that *Borrelia miyamotoi* disease occurs nationwide in Japan☆

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ABSTRACT

Since 2011, *Borrelia miyamotoi* disease (BMD) has been reported in five countries in the northern hemisphere. The causative agent of BMD is transmitted by *Ixodes* ticks, which are also vectors of Lyme disease borreliae. In this study, we examined 459 cases of clinically suspected Lyme disease (LD group), and found twelve cases that were seropositive for the glycerophosphodiester phosphodiesterase (GlpQ) antigen derived from *B. miyamotoi*. The retrospective surveillance revealed that the seroprevalence of anti-GlpQ in the LD group was significantly higher than in a healthy cohort. Seropositive cases were observed from spring through autumn when ticks are active, and the cases were geographically widespread, being found in Hokkaido-Tohoku, Kanto, Chubu, Kinki, and Kyushu-Okinawa regions. Seropositive cases for GlpQ were most frequent in the Chubu region (6.3%) where *B. miyamotoi* has been found in *Ixodes* ticks. Out of the twelve cases that were found in the LD group, three cases exhibited concomitant seropositivity to Lyme disease borreliae by western blot assay. This is the first report of serological surveillance for BMD in Japan, and we conclude that BMD occurs nationwide.

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1. Introduction

Relapsing fever (RF) and *Borrelia miyamotoi* disease (BMD) are caused by infection with spirochetes of the genus *Borrelia*. The causative agents of RF are transmitted by the human louse or Argasid ticks, and RF is mainly reported in the Afrotropic and Palearctic ecozones [1]. Louse-borne RF was endemic in Japan before World War II [2]; however, no indigenous cases have been reported in recent decades [3]. BMD, tentatively referred to as an emerging RF, is caused by infection with *B. miyamotoi*. Patients with BMD generally present with acute, nonspecific, flu-like symptoms, such as fever, headache, general malaise, myalgia, and arthralgia. However recurrent fever, a characteristic symptom of RF, is rare in BMD [4–6]. Human infection was first reported in 2011 in Russia [5]. Since then, patients have been reported in the United States, the Netherlands, Germany, Russia, and Japan [7–12]. *B. miyamotoi* is transmitted by prostriate ticks of the genus *Ixodes* in Asia, Russia, Europe, and North America [13]. The BMD agent, *B. miyamotoi*, has been detected in three species of *Ixodes* ticks in Japan [14,15]: *Ixodes persulcatus*, the main vector of Lyme disease borreliae (*Borrelia garinii*, *Borrelia afzelii*, and *Borrelia bavariensis*) is found in Hokkaido and the mountainous regions of Kanto and Chubu regions [16,17], *Ixodes pavlovskyi*, a rare tick species in Japan [15], and *Ixodes ovatus*, which is found throughout Japan and occasionally attaches to humans [18].

Previously, we reported two cases of concomitant BMD infection in patients with Lyme disease [11]. Moreover, *B. miyamotoi* is known to share a transmission vector tick with Lyme disease borreliae [13]. Therefore, while the clinical features of BMD are still unclear, we hypothesized that Lyme disease or suspected Lyme disease cases would be an appropriate cohort for the study of BMD. In this study, epidemiological characteristics of human BMD were investigated and compared to a healthy cohort. We used a two-step *B. miyamotoi* glycerophosphodiester phosphodiesterase (GlpQ) antigen-based antibody assay to test archived sera from confirmed and suspected Lyme disease patients nationwide.

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2. Materials and methods

2.1. Serum specimens used in this study

2.1.1. Suspected lyme disease cases

Sera were obtained from patients who were clinically suspected of Lyme disease (designated as "LD group") from 2005 through 2012. A total of 459 patients were included in the group, and 221 (48.1%) of them were male. The mean age was 47 years (range, 1–84 years). Age group, sex, and residence of patients by region are listed in Table 1. Sera from patients were stored at −20 °C until use. Laboratory diagnosis for Lyme disease, immunoblotting was performed for these patients by using a commercial kit, recomBlot borreliae IgM/IgG or recomLine borreliae IgM/IgG (Mikrogen GmbH, Neuried, Germany). Decisions on seropositivity were made based on the manufacturer's instructions.

2.1.2. Healthy control

Sera from healthy 542 individuals was used for this cohort. These control sera were provided from the National Serum Reference Bank [National Institute of Infectious Diseases (NIID), Tokyo, Japan]. The ratio of control sera was adjusted for the age group, sex, and region of patient residence to match the LD group (Table 1).

Table 1
Age, sex and locales of individuals used in this study.

Locales and Age of individuals	Lyme disease/suspected Lyme disease			Healthy control	
	Male	Female	Not reported	Male	Female
Hokkaido-Tohoku[a]					
≦10	1	2	0	3	3
11–20	3	1	0	3	2
21–30	5	3	0	5	4
31–40	4	3	0	8	7
41–50	5	2	0	8	7
51–60	9	4	0	10	8
61–70	10	4	0	11	8
≧71	7	2	0	3	2
Not reported	1	0	20	0	0
Subtotal	45	21	20	51	41
Kanto[b]					
≦10	7	6	0	7	5
11–20	2	2	0	6	5
21–30	13	6	0	10	8
31–40	8	17	0	17	13
41–50	11	15	0	17	13
51–60	11	10	0	20	15
61–70	11	7	0	22	17
≧71	4	6	0	14	11
Not reported	7	6	17	0	0
Subtotal	74	75	17	113	87
Chubu[c]					
≦10	0	1	0	3	2
11–20	0	2	0	2	2
21–30	2	2	0	4	3
31–40	6	5	0	7	5
41–50	9	0	0	7	5
51–60	11	4	0	8	6
61–70	3	5	0	9	7
≧71	3	4	0	6	4
Not reported	2	2	2	0	0
Subtotal	36	25	2	46	34
Kinki[d]					
≦10	2	5	0	2	2
11–20	1	2	0	2	2
21–30	5	3	0	4	2
31–40	1	1	0	6	4
41–50	2	5	1	6	4
51–60	5	4	0	7	5
61–70	2	0	0	7	6
≧71	5	6	0	4	3
Not reported	1	2	9	0	0
Subtotal	24	28	10	38	28
Chugoku-Shikoku[e]					
≦10	0	1	0	2	1
11–20	2	1	0	1	1
21–30	1	2	0	2	1
31–40	2	1	0	4	3
41–50	3	0	0	4	3
51–60	0	1	0	5	3
61–70	5	3	0	5	4
≧71	4	0	0	3	2
Not reported	0	0	4	0	0
Subtotal	17	9	4	26	18
Kyushu-Okinawa[f]					
≦10	0	0	0	2	2
11–20	2	1	0	2	1
21–30	1	0	0	3	2
31–40	5	0	1	5	4
41–50	4	4	0	5	4
51–60	5	7	0	6	5
61–70	6	7	0	7	5
≧71	2	4	1	4	3
Not reported	0	1	1	0	0
Subtotal	25	24	3	34	26
Total No.	221	182	56	308	234
		459		542	
Age, average (range)		47 (1–84)		46 (0–87)	
Sex, Male: Female		1.2: 1		1.3: 1	

[a] Hokkaido-Tohoku includes 7 prefectures: Akita, Aomori, Fukushima, Hokkaido, Iwate, Miyagi, and Yamagata.
[b] Kanto includes 7 prefectures: Chiba, Gunma, Ibaraki, Kanagawa, Saitama, Tochigi, and Tokyo.
[c] Chubu includes 9 prefectures: Aichi, Fukui, Gifu, Ishikawa, Nagano, Niigata, Shizuoka, Toyama, and Yamanashi.
[d] Kinki includes 7 prefectures: Hyogo, Kyoto, Mie, Nara, Osaka, Shiga, and Wakayama.
[e] Chugoku-Shikoku includes 9 prefectures: Ehime, Hiroshima, Kagawa, Kochi, Okayama, Shimane, Tokushima, Tottori, and Yamaguchi.
[f] Kyushu-Okinawa includes 8 prefectures: Fukuoka, Kagoshima, Kumamoto, Okinawa, Oita, Miyazaki, Nagasaki, and Saga.

2.2. Preparation of recombinant glycerophosphodiester phosphodiesterase (rGlpQ) antigen

B. miyamotoi strain FR64b was cultivated using BSK-M medium at 30 °C as previously described [15]. Total DNA was purified using Wizard genomic DNA purification kit (Promega, WI, USA), and KOD FX DNA polymerase (TOYOBO Co., LTD., Osaka, Japan) was used for PCR amplification. PCR primers 1065 (5′-GACGACCGACAAGAAA-CAAGAAATGGGTTCAAA-3′) and 1066 (5′-GAGGAGAAGCCCGGTT-ATTTTTTTATGAAGTTCA-3′) were used for DNA amplification of the GlpQ gene (*glpQ*). The underlined portion of each DNA primer was a linker sequence for ligase-independent cloning to plasmid DNA. The amplified DNA fragment was purified using the High pure PCR product purification kit (Merck, Kenilworth, NJ, USA) and was used for in-fusion cloning with plasmid vector, pET46 Ek/Lic (Merck). *E.coli* strain Rosetta™(DE3)pLysS (Merck) was used for expression of the N-terminal His-tagged rGlpQ antigen. Cobalt resin was used to purify the rGlpQ according to the manufacturer's instructions (Takara Bio, Shiga, Japan). The purity of rGlpQ was assessed by SDS-PAGE and Coomassie brilliant blue stain [19,20], and reactivity to anti-His tag monoclonal antibody (Medical & Biological Laboratory Co. Ltd., Aichi, Japan). Quantification of purified rGlpQ was performed with the BCA protein assay kit according to the manufacturer's instructions (Thermo Fisher Scientific Inc., MA, USA). The

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