REVIEW

Borrelia miyamotoi infection in nature and in humans

P. J. Krause[1,2], D. Fish[1], S. Narasimhan[2] and A. G. Barbour[3]

1) *Yale School of Public Health,* 2) *Yale School of Medicine, New Haven, CT and* 3) *University of California Irvine, Irvine, CA, USA*

Abstract

Borrelia miyamotoi is a relapsing fever *Borrelia* group spirochete that is transmitted by the same hard-bodied (ixodid) tick species that transmit the agents of Lyme disease. It was discovered in 1994 in *Ixodes persulcatus* ticks in Japan. *B. miyamotoi* species phylogenetically cluster with the relapsing fever group spirochetes, which usually are transmitted by soft-bodied (argasid) ticks or lice. *B. miyamotoi* infects at least six *Ixodes* tick species in North America and Eurasia that transmit Lyme disease group spirochetes and may use small rodents and birds as reservoirs. Human cases of *B. miyamotoi* infection were first reported in 2011 in Russia and subsequently in the United States, Europe and Japan. These reports document the public health importance of *B. miyamotoi,* as human *B. miyamotoi* infection appears to be comparable in frequency to babesiosis or human granulocytic anaplasmosis in some areas and may cause severe disease, including meningoencephalitis. The most common clinical manifestations of *B. miyamotoi* infection are fever, fatigue, headache, chills, myalgia, arthralgia, and nausea. Symptoms of *B. miyamotoi* infection generally resolve within a week of the start of antibiotic therapy. *B. miyamotoi* infection should be considered in patients with acute febrile illness who have been exposed to *Ixodes* ticks in a region where Lyme disease occurs. Because clinical manifestations are nonspecific, etiologic diagnosis requires confirmation by blood smear examination, PCR, antibody assay, *in vitro* cultivation, and/or isolation by animal inoculation. Antibiotics that have been used effectively include doxycycline for uncomplicated *B. miyamotoi* infection in adults and ceftriaxone or penicillin G for meningoencephalitis.

Keywords: *Borrelia miyamotoi*, *Ixodes*, Lyme disease, relapsing fever, spirochete, tick-borne disease

Article published online: XXX

Corresponding author: P. J. Krause, Yale School of Public Health, 60 College Street, New Haven, CT 06520, USA

Corresponding author: A. G. Barbour, Departments of Medicine and Microbiology and Molecular Genetics, 3012 Hewitt, University of California Irvine, Irvine, CA 92660, USA

E-mails: peter.krause@yale.edu **(P.J. Krause),** abarbour@uci.edu **(A.G. Barbour)**

Introduction

Borrelia miyamotoi is a relapsing fever spirochete transmitted by the same hard-bodied (ixodid) ticks that are vectors of *Borrelia burgdorferi* and other Lyme disease agents [1–10]. As early as 1985, spirochetes that were likely *B. miyamotoi* were observed in ticks in the United States. They were mistakenly thought to be *B. burgdorferi* as a consequence of cross-reactive antibodies that were used in direct immunoassays. For example, two reports identified putative *B. burgdorferi* in *Ixodes scapularis* and *Ixodes pacificus* adult ovarial tissue, eggs and/or larvae [11,12]. This led to the false conclusion that *B. burgdorferi* was transovarially transmitted by ticks. Recent experimental evidence has confirmed transovarial (vertical) transmission of *B. miyamotoi* but not *B. burgdorferi* in *I. scapularis* [13]. Misidentification not only led to false conclusions about the transovarial transmission of *B. burgdorferi* in *Ixodes* ticks but may have delayed recognition of *B. miyamotoi* as an etiologic agent.

It was not until 1994 that spirochetes identified as *B. miyamotoi* were isolated from field-collected *Ixodes persulcatus* ticks and the small Japanese field mouse *Apodemus argenteus* in Japan [1]. In 2000 a novel spirochete was serendipitously identified in laboratory-reared *I. scapularis* ticks that were expected to be free from *B. burgdorferi* infection. Sequencing of the 16S ribosomal gene and other loci revealed that this newly discovered organism from the northeastern United States was closely related to *B. miyamotoi* isolates of Japan [2,4]. *B. miyamotoi* has subsequently

http://dx.doi.org/10.1016/j.cmi.2015.02.006

been identified in all other tick species that are vectors of Lyme disease and probably occurs throughout much of the Holarctic region [2–10,13–30]. The discovery of *B. miyamotoi* expands the potential geographic range of relapsing fever group *Borrelia* species. Most other relapsing fever spirochetes are transmitted by soft-bodied ticks (Argasidae) and lice that have different ecologies and only occasionally are found in the same geographic locations as Lyme disease vectors [31].

Although the novelty and wide geographic distribution of *B. miyamotoi* have been recognized for several years now, this spirochete received comparatively little attention until human cases of a relapsing fever–like disease from *B. miyamotoi* infection were reported in 2011 in Russia and subsequently in the United States, Europe and Japan [10,32–38]. These reports have documented the public health importance of *B. miyamotoi*. Human *B. miyamotoi* infection appears to be comparable in frequency to babesiosis or human granulocytic anaplasmosis (HGA) in the northeastern United States and may cause severe disease, including meningoencephalitis in immunocompromised individuals, as well as coinfection with other *Ixodes*-borne pathogens [10,32–38]. Additionally, antigenic cross-reactivities in immunoassays between *Borrelia* species in North America may complicate diagnosis of both Lyme disease and relapsing fever [39].

The organism

B. miyamotoi was not the first relapsing fever group species shown to use a hard-bodied tick species as its primary vector. The association of the cattle pathogen *B. theileri* with *Boophilus* (now named *Rhipicephalus*) *microplus* hard-bodied ticks was noted by Arnold Theiler a century ago [40]. More recently, *B. lonestari* was discovered in *Amblyomma* species [41], and the reptile pathogen *B. turcica* was shown to be transmitted by *Hyalomma* species hard-bodied ticks [42]. Nucleotide sequences of these organisms, including the complete chromosomes of isolates of *B. miyamotoi* from North America [43] and Japan (GenBank accession number CP004217), confirmed that *B. miyamotoi* and the other hard-bodied tick–associated species phylogenetically cluster with the relapsing fever *Borrelia* species [44]. These include both New World species *B. hermsii* and *B. turicatae* and the Old World species, such as *B. crocidurae,* which are transmitted by soft-bodied ticks (Fig. 1). A real-time quantitative PCR based on the same primers but different probes for the 16S ribosomal RNA gene distinguishes between the relapsing fever group species (including *B. miyamotoi*) and the Lyme disease group species [45].

Differences exist between *B. miyamotoi* isolates according to tick vector and geographic region, but so far, little genetic difference has been found between isolates within a given geographic area or with the same tick vector association [4,18,29]. The overall genetic difference between a North American *B. miyamotoi* isolate (LB-2001) and a Japanese *B. miyamotoi* isolate (FR64b) is about the same as between *B. turicatae* and *B. parkeri,* two North American relapsing fever species with different host and vector associations [31], but less than between the two major genomic groups of *B. hermsii* strains [46] (Fig. 1). In our opinion, the designation *sensu lato* is provisionally applicable for the North American strains, with *sensu*

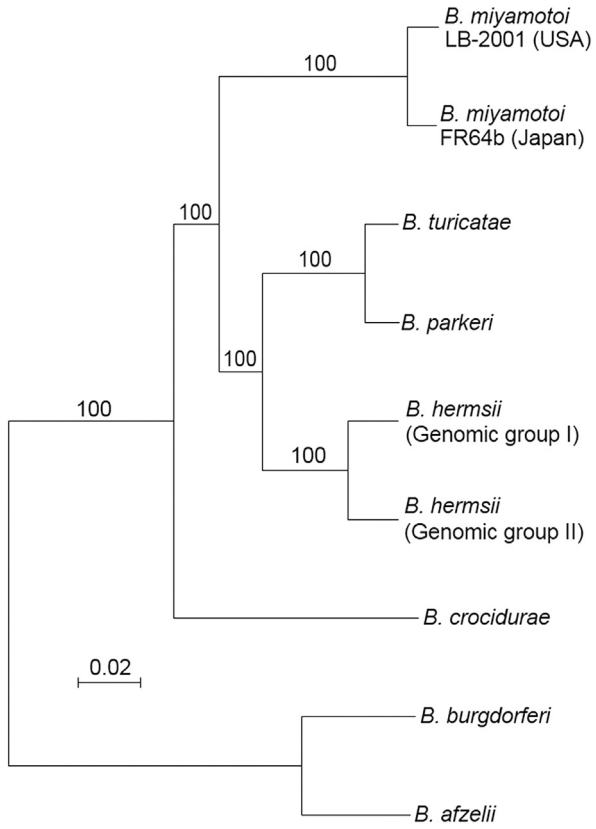

FIG. 1. Phylograms of aligned syntenic chromosome sequences of nine selected relapsing fever group and Lyme disease group *Borrelia* species by BioNJ neighbor-joining protocol for observed differences at 850,377 ungapped sites by a procedure described elsewhere [44]. Nodes with bootstrap values of ≥70% support after 100 replicates are shown. Bar represents nucleotide substitutions per site. The organisms (with GenBank accession numbers) were *B. miyamotoi* strain LB-2001 from Connecticut, USA (CP006647); *B. miyamotoi* strain FR64b from Japan (CP004217); North American tick-borne relapsing fever species *B. turicatae* strain 91E135 (CP000049); *B. parkeri* strain HR1 (CP007022); *B. hermsii* strain DAH of genomic group I (CP000048); *B. hermsii* strain YOR of genomic group II (CP004146); Old World tick-borne relapsing fever species *B. crocidurae* strain DOU (CP004267); and two Lyme disease species, *B. burgdorferi* strain B31 (AE000783) and *B. afzelii* strain PKo (CP002933).

Please cite this article in press as: Krause PJ, et al., *Borrelia miyamotoi* infection in nature and in humans, Clinical Microbiology and Infection (2015), http://dx.doi.org/10.1016/j.cmi.2015.02.006