Borrelia miyamotoi: A Lesson in Disease Discovery

Recognition of novel infectious diseases has historically followed a prescribed course, which starts by defining a clinical syndrome. A prototypical example was the discovery of Lyme disease during the 1970s, which began with the description of epidemic oligoarticular arthritis (1), eventually followed by identification of the causative agent (2). In this issue, Chowdri and colleagues (3) contribute to the unfolding description of Borrelia miyamotoi infection—an illness with some similarities to Lyme disease but that was identified by reversing the traditional approach to disease discovery.

In 1995, a novel Borrelia species was isolated from the hard (ixodid) tick vector of Lyme disease in Japan (4). Borrelia miyamotoi was later detected in ixodid ticks in North America (5, 6) and Eurasia (7–9), which established its widespread geographic presence and reconfirmed its ecological niche within vectors of Lyme disease despite its closer phylogenetic similarity to relapsing-fever borreliae (4). Investigators subsequently began searching for human cases.

In 2011, B. miyamotoi infection was detected in 46 Russian patients by using species-specific polymerase chain reaction (PCR) (9). In this series, all patients reported a recent tick bite and were hospitalized with influenza-like illness characterized by fever, headache, fatigue, myalgia, proteinuria, and elevated hepatic aminotransferase levels (9). A 2-week course of ceftriaxone or doxycycline reportedly provided effective treatment (9).

Cases were first described in North America in 2013 (10, 11). Serologic evidence of B. miyamotoi infection was detected among symptomatic and asymptomatic persons living in Lyme disease–endemic regions of the northeastern United States (10). Some symptomatic patients presented with a viral-like illness similar to that described in the Russian cohort, and several had Lyme disease or babesiosis co-infection (10). Separately, B. miyamotoi meningoencephalitis was reported in an elderly, immunocompromised woman from rural New Jersey (11). In this case, the spirochete was directly visualized in cerebrospinal fluid by microscopy and was also detected by PCR (11).

Chowdri and associates (3) provide further evidence of human B. miyamotoi infection in the northeastern United States. The diagnosis was established using PCR on whole-blood samples collected during the acute phase of illness, similar to the methods used in Platonov and coworkers’ report (9). These cases further delineate the clinical syndrome associated with B. miyamotoi infection in immunocompetent adults.

Although Chowdri and coworkers’ article provides us with a better understanding of human B. miyamotoi infection, many questions remain unanswered. In particular, the full spectrum of illness needs to be defined. To date, the description of B. miyamotoi infection is based on the presentation of severely ill hospitalized patients, and whether severe illness is typical remains to be determined. The extent to which B. miyamotoi infection resembles relapsing fever is also unclear; a proportion (11%) of the Russian cases had this syndrome (9) but neither patient described by Chowdri and colleagues did.

Although B. miyamotoi meningoencephalitis may occur in immunocompromised hosts, whether B. miyamotoi is neurotropic or causes central nervous system infection with any frequency, particularly when immunity is intact, is unknown. Finally, disease prevalence is undetermined and may be quite low, considering that the proportion of ixodid ticks carrying the agent in the United States is reportedly 10-fold less than those carrying Lyme disease–associated borreliae (5).

Indeed, by attempting to define novel human infections in reverse order—first identifying infectious agents in a known vector, then searching for human disease correlates—investigators risk detecting agents for which no human correlate exists. On the other hand, this approach almost certainly accelerated discovery of human B. miyamotoi infection, because its clinical features seem to overlap substantially with those of human anaplasmosis and other tickborne infectious diseases, making identification as a human pathogen by the conventional approach unlikely. This reverse strategy will no doubt become a model for future discovery of novel infectious diseases.

As the body of literature describing human infection with B. miyamotoi expands, one can predict that there will be increasing demand from patients and clinicians for diagnostic tests, especially because effective therapy may be available. Direct detection of the organism in cerebrospinal fluid is evidently possible in meningoencephalitis (11), but whether blood smear examination will be useful in diagnosing non–central nervous system infection, as it is in relapsing-fever borreliosis, is unclear.

Of interest, serologic testing for Lyme disease may prove useful as a “surrogate marker” for B. miyamotoi infection until organism-specific assays become available for routine clinical use. In the Russian series, all case patients had positive results on a European Lyme enzyme-linked immunosorbent assay designed to detect IgM antibodies against Lyme disease–associated spirochetes (9). Furthermore, 1 of the 2 cases presented by Chowdri and associates seroconverted by Lyme IgM capture enzyme immunoassay and IgM Western blot analysis between the acute and convalescent phases of illness. However, the latter finding may indicate co-infection by B. burgdorferi, rather than cross-reactivity from B. miyamotoi, and the apparent cross-reactivity noted in the Russian series by using a European Lyme enzyme-linked immunosorbent assay may not necessarily occur using assays designed for use in other geographic regions.
Notably, the patient with *B. miyamotoi* meningoencephalitis had negative results on a U.S. Lyme capture enzyme immunoassay in the acute and convalescent phases of illness (11). Thus, further investigation is needed before serologic assays for Lyme disease can be recommended to evaluate patients with suspected *B. miyamotoi* infection.

Considering that agent-specific PCR and serologic tests have been developed for research purposes (9, 10), the question arises: Should we rush to make them widely available? In our opinion, that would be premature. It seems most appropriate for local and regional public health laboratories, along with investigators, to develop and offer diagnostic testing for the purpose of studying the disease. Once the infection is better understood, diagnostic testing can transition to the clinical laboratory to support the care of individual patients. In the meantime, *B. miyamotoi* infection should be included in the differential diagnosis of patients presenting in Lyme disease–endemic areas with unexplained fever, headache, myalgia, elevated hepatic aminotransferase levels, and leukopenia or thrombocytopenia during the summer months, and empirical doxycycline should be considered in severely ill patients.

John A. Branda, MD  
Eric S. Rosenberg, MD  
Massachusetts General Hospital  
Boston, Massachusetts

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Requests for Single Reprints: Eric S. Rosenberg, MD, Massachusetts General Hospital, Infectious Disease Division, Gray J-504, 55 Fruit Street, Boston, MA 02114.

Current author addresses are available at www.annals.org.


References

Current Author Addresses: Dr. Branda: GRB-526 Microbiology, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114. Dr. Rosenberg: Massachusetts General Hospital, Infectious Disease Division, Gray J-504, 55 Fruit Street, Boston, MA 02114.