WILDERNESS & ENVIRONMENTAL MEDICINE 2021; 32(2): 240–6

REVIEW ARTICLE

Underrecognized Tickborne Illnesses: *Borrelia Miyamotoi* and Powassan Virus

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Over the past 2 decades, tickborne disease has been increasingly recognized as a threat to humans as a result of the growing geographic range of ticks. This review describes 2 tickborne diseases, *Borrelia miyamotoi* and Powassan virus, that likely have a significant impact on humans, yet are underdiagnosed compared to most other tickborne diseases. We performed a literature search from 2015 to 2020. *Borrelia miyamotoi* is a tickborne pathogen that infects and co-infects ticks along with other pathogens, including *Borrelia burgdorferi*. Because *B miyamotoi* infects the same *Ixodes* ticks as *B burgdorferi*, *B miyamotoi* may cover a similar geographic range. *B miyamotoi* infection may be underdiagnosed for 2 reasons. First, a presumptive treatment approach to Lyme disease may result in *B miyamotoi* infection treatment without identification of the actual cause. Second, the absence of readily available testing and diagnostic criteria makes it difficult to diagnose *B miyamotoi* infection. Powassan virus is a tickborne flavivirus similar to the dengue virus. Powassan virus disease appears to have an asymptomatic or minimally symptomatic presentation in most people but can cause devastating and fatal encephalitis. The Powassan virus may be transmitted in less than 15 min of tick feeding. Powassan virus disease is a difficult diagnosis because testing capabilities are limited and because there may be co-infection with other tickborne pathogens.

Keywords: relapsing, fever, encephalitis, flavivirus, spirochete, Ixodes

Introduction

Over the past 2 decades, the public health threat posed by ticks has increased significantly and results from greater exposure of the human population to the expanding geographic range of ticks.[1] This human exposure is multifactorial and includes the increased spread of humans to suburban areas, increased use of outdoor areas, and greater tick populations. The discovery of several new tickborne human pathogens has increased awareness and recognition of more diseases spread by ticks.

Over the past 13 y, the number of cases of tickborne diseases reported in the United States has more than doubled, with state and local health departments reporting a record number of cases of tickborne conditions to the Centers for Disease Control and Prevention.[2] The reported number of cases of Lyme disease, anaplasmosis, ehrlichiosis, spotted fever rickettsioses (including Rocky Mountain spotted fever), babesiosis, tularemia, and Powassan virus disease increased from a total of 48,610 reported cases in 2016 to a total of 59,349 reported cases in 2017.[3] These reported cases likely capture only a fraction of the overall number of people with tickborne illnesses.[3]

In this review, we describe 2 tickborne diseases that are less familiar and uncommonly diagnosed yet have potential morbidity and mortality owing to limited diagnostic criteria and testing: *Borrelia miyamotoi* and Powassan virus disease. We chose to discuss *B miyamotoi* because it is likely a more prevalent disease than currently known, and recognition is challenging because there are no diagnostic criteria and there is no widely available test. This could result in physicians overlooking this infection and failing to treat a patient properly if other more recognized infections such as Lyme, babesiosis, rickettsioses, anaplasmosis, and ehrlichiosis are ruled out by testing that is widely available. We chose to review the Powassan virus because it only requires 15 min of tick attachment for transmission, and the sequelae of the neurologic disease are devastating, in addition to a 10% mortality rate.

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Submitted for publication August 2020.
Accepted for publication January 2021.

Methods

We performed a literature search capturing 2015 to 2020 in Embase, MEDLINE, and Cochrane Database using the keywords *Borrelia miyamotoi*, Powassan virus, humans, epidemiology, and clinical presentation. This search was limited to these years because we had performed previous research on the topic but did a recent formal review to ensure complete information.

BORRELIA MIYAMOTOI

What is it?

Borrelia miyamotoi is the causative agent of *Borrelia miyamotoi* disease (BMD). *Borreliae* are long, highly motile corkscrew-shaped bacteria that are part of the spirochete phylum. The genus *Borrelia* comprises the Lyme disease group (*Borrelia burgdorferi* and other similar spirochete species) and the relapsing fever group (including *B hermsii*, *B turicatae*, *B parkeri,* and *B miyamotoi*). Although other tickborne relapsing fever spirochetes infect the soft-body ticks of the *Ornithodoros* genus, *B miyamotoi* is the exception: It infects the hard-shell *Ixodes* tick that also carries *B burgdorferi*.

When was it discovered?

B miyamotoi was first isolated from an *Ixodes* tick in Japan in 1995.[4] The first description of human infection was a Russian case series in 2011.[5] Since then, human cases have been reported elsewhere in Europe, China, and the United States in 2013.[6-9] *B miyamotoi* has been found in various *Ixodes* ticks, including *I scapularis* (also called black-legged or deer tick) in the northeastern and northern midwestern United States, *I pacificus* in California, *I ricinus* in Europe, and *I persulcatus* in Europe and Asia.[4,10-13]

How is it transmitted?

The *Ixodes* ticks have increased their geographic range in the past decade[14,15] owing to human and natural factors,[13] such as land use, climate change, and change in vector populations. The geographic range of BMD is not well described, but it likely mirrors Lyme disease, with about 2% of *Ixodes* ticks carrying the spirochete.[16,17] *I scapularis* is documented in 1420 (45.7%) of the 3110 continental United States counties.[15] *Ixodes* ticks can be co-infected with multiple pathogens and can transmit more than 1 pathogen.[18-20] One study evaluating patients in California found antibody seropositivity with *B burgdorferi* in 33%, relapsing fever *Borrelia* in 27%, and both in 11%.[21] This suggests that co-infection is possible and that the prevalence of *B miyamotoi* and other relapsing fever *Borrelia* species may be underestimated. *B miyamotoi*, unlike *B burgdorferi*, can be maintained both transstadially (persisting through different life stages of the tick) and transovarially (passing from parent to offspring via the ovaries) within a host tick.[22] The tick can transmit *B miyamotoi* at any stage of life, resulting in a possibility of human infection throughout a more significant part of the year than Lyme disease.[23] Ticks become infected with *B burgdorferi* by feeding on an infected host, which usually occurs at the larval stage. They then take a second feeding the next spring, when they are likely to transmit *B burgdorferi.* For *B miyamotoi,* the relation to tick stage is less critical. The tick may hatch already infected with and able to transmit *B miyamotoi*. This means it may transmit *B miyamotoi* with the first feeding as a larva in spring, summer, or fall and later in its nymphal and adult stages.

How long does the tick have to be attached to transmit Borrelia miyamotoi?

Nymphs that are transovarially infected with *B miyamotoi* harbor the spirochetes in their salivary glands before attaching to a host. This allows for rapid transmission.[24] *B miyamotoi* can be transmitted 10% of the time within the first 24 h of attachment, increasing steadily to reach 73% for a complete feeding.[24] There is no evidence of transmission of *B burgdorferi* in the first 24 h of attachment and only 10% in 48 h.[24] Thus, transmission of *B miyamotoi* is more rapid than transmission of *B burgdorferi*. Understanding this more rapid transmission of infection of *B miyamotoi* may be a consideration in determining prophylactic treatment for tick bites with a shorter time of attachment in endemic areas for *B miyamotoi*. It also underscores the need for frequent tick checks for those exposed to tick infested settings.

Clinical presentation

The original 2011 Russian case series described the symptomatology of 46 patients, including viral-like symptoms of fever (98%), malaise (98%), headache (89%), and myalgias (59%), with onset about 2 wk after a tick bite. Eleven percent had 1 or more recurrent episodes of symptoms, 68% had liver enzyme abnormalities, and 9% had an erythema migrans type rash. Patients generally did well after treatment with ceftriaxone or doxycycline.[5] These disease features were echoed in the 2015 Northeastern United States case series: Patients had a nonspecific febrile illness (96%) with headaches (96%), myalgias (84%), fatigue (82%), and arthralgias (76%), as

well as elevated liver function tests (53%), thrombocytopenia (51%) and leukopenia (43%). Only 8% had a rash. The absence of a rash in conjunction with the leukopenia, thrombocytopenia, and elevated liver function tests found in many tickborne diseases may help to distinguish BMD from Lyme disease.[25]

There are 4 case reports of *B miyamotoi* meningitis in immunocompromised patients and 1 case report in an immunocompetent patient. The cerebrospinal fluid in all cases showed pleocytosis with elevated protein levels.[9,26-28]

Although symptoms and laboratory testing abnormalities in BMD are similar to those of anaplasmosis, patients with anaplasmosis usually defervesce within 24 h after starting doxycycline. BMD should be considered for patients with presumed anaplasmosis who do not improve within 24 h after the initiation of antibiotics.[29] Tickborne relapsing fever usually presents with multiple febrile episodes that correspond to peak spirochete loads in the blood. With BMD, the highest number of reported relapsing events after the initial fever was 2.[5] Although more relapsing febrile events may have occurred in untreated patients, the natural history of febrile events may be underestimated because many patients received empiric treatment after exposure to ticks.[5]

Making the diagnosis

Making a definitive diagnosis of BMD is challenging. Suspicion should be based on clinical features, geographic location, time of year, and exposure to ticks. Many patients may not be aware of an inciting bite because of the very small size of tick larvae and nymphs that can still spread the infection. No test specific to *B miyamotoi* has been approved by the United States Food and Drug Administration as of October 2020. Although several testing options for other *Borrelia* species are available, there is potential for cross-reactivity. Serologic testing cannot accurately differentiate between acute and past infections and may be less likely to be positive during the initial infectious phase.[30] Blood smears are not sensitive enough to consistently confirm the presence of *B miyamotoi* when there is a positive antigen test.[31]

Serologic testing of *B miyamotoi* IgM and IgG antibodies is possible by a few commercial laboratories.[13] Depending on the test chosen, it is possible to differentiate *B miyamotoi* from *B burgdorferi*.[32] However, other tests for *B burgdorferi* might allow for a cross reaction with *B miyamotoi*. This could lead to an incorrect diagnosis of Lyme disease in a patient who actually has BMD.[33,34]

The most specific test currently available in several public health and commercial laboratories is polymerase chain reaction (PCR) testing of blood or cerebrospinal fluid for the *B miyamotoi* GlpQ enzyme. When interpreting the test results, consideration must be given to other endemic relapsing fever spirochetes present in the area. These other spirochetes may give a false-positive test result for *B miyamotoi*. PCR testing does provide the benefit of directly confirming an acute infection, rather than relying on detection of an antibody response to the pathogen. However, accessibility is still very limited. One test using this approach, the TBD serochip, is an array-based assay testing for 8 different tickborne diseases, including *B miyamotoi*. Developed in 2018, it is promising but has not yet become widely available.[35]

Treatment

There is no clear evidence-based treatment for *B miyamotoi*. The use of doxycycline as the primary therapeutic agent has been derived empirically from the treatment of *B burgdorferi* and has shown success in the published literature.[5,6,26] In vitro analysis has shown the susceptibility of *B miyamotoi* to ceftriaxone, azithromycin, and doxycycline, with resistance to amoxicillin.[36]

POWASSAN VIRUS

What is it?

Powassan virus is a flavivirus that encodes for a single polypeptide that replicates in host cells.[37] Other more commonly known diseases caused by flaviviruses include dengue, yellow fever, West Nile encephalitis, and tickborne encephalitis (primarily found in Europe). Other tickborne viruses that have been recently discovered in the United States are the Heartland virus and the Bourbon virus. The Heartland virus is a phlebovirus first discovered as a cause of human illness in 2009 in Missouri.[38] The Bourbon virus is a thogotovirus discovered in the United States in 2017 that has been identified in the Midwest and the southern United States.[39]

Powassan virus is 1 of 6 mammalian tickborne flaviviruses. It exists in 2 lineages: the prototype Lineage I Powassan virus and Lineage II, called the deer tick virus. The deer tick virus is very similar genetically to the Powassan virus. The clinical presentation of Powassan virus and the deer tick virus infection are the same.[40] For this review, Powassan (POW) virus refers to both the Powassan virus and the deer tick virus, and Powassan virus disease (PWVD) refers to the clinical presentation from infections caused by each of these viruses.

When was it discovered?

Powassan virus is named for the Ontario, Canada, town where it was first isolated from the brain of a 5-y-old boy who died of severe encephalitis in 1958.[41] It was later

identified in New Jersey in 1970 and in Eastern Russia in 1978.[42,43] PWVD has not been reported in any other country. In the United States, in the years 2014 to 2019, there were 7, 6, 21, 33, 21, and 37 cases recorded by the Centers for Disease Control. In 2019, 13 US states reported cases: Connecticut, Indiana, Massachusetts, Maine, Minnesota, North Carolina, North Dakota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Wisconsin.[44]

How is it transmitted?

The hard-bodied *Ixodes* ticks are the vector for the POW virus. *I cookei*, the groundhog tick, and *I scapularis* are the principal vectors. *I cookei* usually lives in burrows or nests and only travels on its host groundhogs and skunks when they move to new burrows.[45] *I cookei* rarely feeds on humans, probably because it has less exposure to humans than other tick species. Therefore, it has been relatively difficult to study. In contrast, *I scapularis* ticks are more easily harvested and easier to study. *I scapularis* ticks in their larval form feed on the white-footed mouse, which is thought to be the primary reservoir of the POW virus. The nymphs feed on small mammals, birds, reptiles, and humans. The adult females feed primarily on larger animals such as deer and livestock.[13] Studies of wild *I scapularis* populations have shown a POW virus infection rate in the range of 0 to 5%.[46,47] Human exposure is thought to be increasing with the expanding geographic range of *I scapularis*.[48]

In experimental conditions, the transmission of POW virus from viremic hosts to adult *I scapularis* females occurred at a rate of 57%. Infected ticks at any life stage can transmit the POW virus to new hosts.[49] Although many flaviviruses have mosquitos as competent vectors, there is no evidence of human POW virus disease transmitted by mosquitos, nor is there evidence that mosquitos are a competent vector for transmission to humans.[50]

POW virus has been shown to co-infect *I scapularis* ticks along with many other diseases, such as *B burgdorferi*, *Anaplasma phagocytophilum*, *B miyamotoi*, and *Babesia microti*.[20,47] *Ixodes* ticks also transmit *Ehrlichia* species and have potential for co-infection with POW virus, although this has not yet been reported. Unfortunately, much of the virome of ticks has been unknown until recently, and the scope of human disease caused by these is largely undiscovered.[51]

How long does the tick have to be attached to transmit the Powassan virus?

POW virus differs from many tickborne pathogens such as *B miyamotoi, B burgdorferi*, *Anaplasma*, and *Babesia microti* because there is no substantial lag time between tick attachment to the host and transmission. This is attributed to the virus already being present in the salivary glands at the time of feeding,[52] as opposed to many other nonviral tickborne diseases that are harbored in the tick's midgut. Transmission in mice has been shown to occur within 15 min of *I scapularis* attachment.[14,52]

Clinical presentation

Few people who become infected with the POW virus have clinically significant disease. However, POW virus can cause serious central nervous system infections, including encephalitis. In a 1962 study of Northern Ontario residents, 11 of 1008 individuals were found to be seropositive for the virus, indicating that they had been previously infected, either asymptomatically or at least without severe disease.[53] The rate of seropositivity was 1% in the entire study population but up to 3% in areas with a higher incidence of known illness.[53] The typical incubation period is 8 to 34 d before the development of a nonspecific viral syndrome of malaise, sore throat, and nausea. After 1 to 3 d, symptoms may worsen to include disorientation, headache, neck stiffness, and fever up to 40°C. The symptoms may be accompanied by clonus, ocular, and other motor palsies, as well as obtundation and convulsions.[54-56] Temporal lobe involvement with symptoms, including olfactory hallucinations, can mimic herpes simplex encephalitis.[57] Neuroinvasive disease is often severe and disabling, with long-lasting neurologic sequelae. Approximately 50% of cases result in lasting hemiplegia, memory problems, and muscle wasting.[56] Ten percent of cases are fatal.[56]

A definitive diagnosis of PWVD can be made by PCR of blood or cerebrospinal fluid. However, the virus can only be detected during the early viremic period. In most cases, this has passed before the onset of neurologic symptoms, severely limiting the ability of PCR to diagnose the disease.[58] IgG by enzyme-linked immunosorbent assay is the mainstay of diagnosis, but confirmation requires specialized testing. Cerebrospinal fluid analysis is consistent with aseptic meningitis. Poliomyelitis-like anterior horn involvement may be seen on magnetic resonance imaging,[59] and changes have been observed on electroencephalogram.[60]

Diagnosis of PWVD can be further complicated by co-infection with other pathogens such as *B burgdorferi*.[61] For example, 1 patient presenting with hemolytic anemia, thrombocytopenia, mild hepatitis, and acute kidney injury later developed a declining mental state, myoclonus, and tremors. The final diagnosis included concurrent Lyme carditis, babesiosis, and Powassan encephalitis.[62] Because illness due to PWVD is

nonspecific, taking a careful history may be vital to making this rare but important diagnosis. The history should include potential exposure to environments where ticks are present.

Treatment

There is no specific treatment for PWVD other than supportive care. Candidate vaccines have so far lacked generalizability, efficacy, or lasting immunity. This highlights the importance of preventing tick bites by avoiding tick-infested areas, wearing appropriate clothing, and using chemical repellant.

Conclusions

Borrelia miyamotoi and Powassan virus, as well as most other tickborne diseases that affect humans, are uncommonly recognized. They are transmitted by many of the same ticks as Lyme disease and may present as a primary infection or a co-infection. One should have a high index of suspicion for these diseases in patients presenting with possible Lyme disease. Unfortunately, at this time, there are no widely available, definitive diagnostic tests or diagnostic criteria for either disease.

Acknowledgments: The authors thank Ms. Alexandria Brackett, MA, MLIS, for her support with the literature search.

Author Contributions: Study concept and design (DD, CD, KG); acquisition of data (DD, CD, KG); analysis and interpretation (DD, CD, KG); drafting of manuscript: DD, CD, KG; critical revisions: DD, CD, KG; all authors approved the final version of the manuscript.

Financial/Material Support: None.

Disclosures: None.

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