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Tick-borne relapsing fever in British Columbia: A 10-year review (2006–2015)

A case review of *Borrelia hermsii* infections in BC indicates physicians outside disease-endemic areas may not be fully aware of the presence of this spirochete in the province.

ABSTRACT

Background: **Tick-borne relapsing fever is one of the oldest tick-borne diseases identified in British Columbia. The causative agent is the spirochete *Borrelia hermsii,* which is transmitted to humans by the night-feeding soft-shelled tick *Ornithodoros hermsi* found in southeastern British Columbia and the northwestern United States. The identification of this illness is made difficult by the fact that tick-borne relapsing fever is not a reportable illness in BC and laboratory diagnosis can be challenging. The innocuous feeding pattern of the vector tick means bites can go unnoticed, while the typical 7-day delay in symptoms means patients often do not become ill until after they have left a disease-endemic area where physicians are more likely to recognize the illness. Identification and treatment of this illness is important because it can cause long-term sequelae, including cardiac and renal disturbances, peripheral nerve disturbances, ophthalmitis, and complications during pregnancy. A report on a 10-year review of cases in BC was proposed to alert physicians to the presence of this infectious disease and explain how to submit blood samples for testing to the BC Centre for Disease Control Public Health Laboratory.**

Methods: **From 2006 to 2015, the BC Centre for Disease Control Public Health Laboratory received 112 samples from 100 patients suspected to have tick-borne relapsing fever. These samples were analyzed using dark field microscopy, immunofluorescence assay, western blot testing, and polymerase chain reaction assay. A review of the laboratory findings was conducted and the diagnostic challenges and sample requirements were considered.**

Results: **The 100 patients (57 male, 43 female) whose 112 samples were analyzed during the review period ranged in age from 6 to 83 years, and most (67%) were either young or middle-aged adults (20 to 60 years). Of these patients, 19 tested positive for *B. hermsii* (12 female, 7 male). Except for 2009 and 2014, at least one case of tick-borne relapsing fever was identified each year, with the top year being 2007 (seven cases). Most of the positive cases were associated with the Thompson-Okanagan region. Polymerase chain reaction assay and Giemsa stain testing yielded the highest proportion of positive results (4 of 11 samples) followed by immunofluorescence assay for IgG antibodies (19 of 109).**

Conclusions: **The high proportion of positive results (19%) may be due to the submission of mainly very characteristic samples received from an endemic area. Many physicians may not be aware of the presence of *B. hermsii* tick-borne relapsing fever in BC and therefore do not request testing. Physicians should note that patients are unlikely to report a painless tick bite received during sleep and that the key symptom is a sudden, high fever (39.2 °C or higher) that follows an incubation period of approximately 7 days and lasts 3 to 7 days. An asymptomatic period of 7 days is then followed by an average of two relapses. General infections considered in the differential diagnosis should include salmonellosis, bartonellosis, tularemia, and leptospirosis. Patients should also be asked about foreign travel to rule out a range of other infections such as malaria, kala azar, yellow fever, and sand fly fever. Blood samples for identifying the causative**

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agent for a recurrent fever should be collected while the patient is febrile and prior to initiation of antibiotic therapy. The appropriate samples are 7 mL of blood in a red-top serum separator tube for serology and 7 mL of blood in an EDTA tube for Giemsa staining and polymerase chain reaction assay. Patients diagnosed with tick-borne relapsing fever have been shown to respond effectively to doxycycline/tetracycline, macrolides such as erythromycin, and penicillin. Approximately one-half of patients will experience some sort of Jarisch-Herxheimer reaction and should be monitored for this. In future, molecular testing, an organized approach to diagnosis, and a greater physician awareness of this illness should allow for more rapid and confident diagnoses and effective treatment of patients with this tick-borne illness.

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Background

The Thompson-Okanagan region of British Columbia (population approximately 540 000 in 2015) is an arid part of the province contiguous with north-central Washington state. A warm dry climate and bountiful natural resources make this region a major tourist destination for outdoor activity. Approximately 40% of visitors come from BC and a similar proportion from other parts of Canada.[1] Since the mid-1930s, there have been several documented cases of tick-borne relapsing fever (TBRF) in the Thompson-Okanagan, eastern Washington, eastern Oregon, and Montana.[2] The causative agent is the spirochete *Borrelia hermsii*, which is transmitted to humans by the painless bite of the night-feeding soft-shelled tick *Ornithodoros hermsi* (**Figure 1**).[3] The identification of TBRF is made difficult by the fact that it is not a reportable illness in BC and laboratory diagnosis can be challenging.[3] As well, the innocuous feeding pattern of the vector tick means that bites can go unnoticed and the typical 7-day delay in symptoms during the incubation period means patients often do not become ill until after they have left a disease-endemic area where physicians are more likely to recognize TBRF.[4,5]

Infection with *B. hermsii* leads to a relapsing fever that may have as many as 13 cycles before resolving over 6 to 7 months. Identification and treatment of this illness is important because it can cause long-term sequelae, including cardiac and renal disturbances, peripheral nerve disturbances, and ophthalmitis.[6-8] Intrauterine transmission is possible and may lead to complications during pregnancy.[9] Generally, death occurs more frequently in untreated louse-borne relapsing fever than in TBRF. Mortality from TBRF in North America is rare, but has been associated with complications during pregnancy, including spontaneous abortion, premature birth, and neonatal death.[8]

The British Columbia Centre for Disease Control (BCCDC) Public Health Laboratory (PHL) currently provides testing services for the diagnosis of *B. hermsii* TBRF. A report on a 10-year review of cases and PHL testing capabilities was proposed to alert physicians to the presence of this infectious disease, provide education on TBRF, and explain how to submit blood samples for testing.

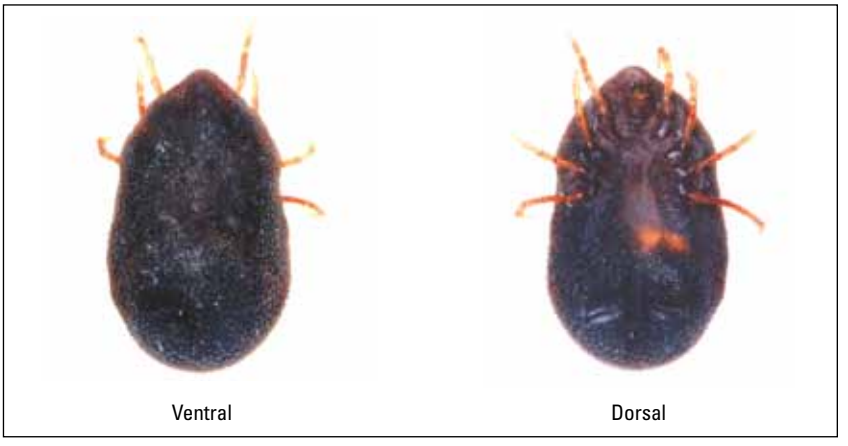

Figure 1. Two views of an *Ornithodoros hermsi* specimen collected in the Thompson-Okanagan region and measuring 5.5-mm long and 3.4-mm wide.

Methods

From 2006 to 2015, the BCCDC Public Health Laboratory received 112 samples for TBRF testing from 100 patients (57 male and 43 female) ranging in age from 6 to 83. The following tests were used to determine if any of the samples contained *B. hermsii*.

Dark field microscopy and Giemsa stain. These procedures were used to visualize spirochetes (Figure 2) in the whole blood of patients collected during a febrile period when the density of spirochetes is at least 10^5 cells per mL of blood.[2]

Immunofluorescence assay (IFA). A two-step sandwich procedure using indirect immunofluorescence was used to detect antibodies to *B. hermsii* HS1 (serotype 33).[5] Samples were considered positive if dilutions of 1:256 or more conferred fluorescence and samples demonstrating reactivity of more than 1+ at dilutions of 1:512 were scored as 1:512 or more.

Western blot test. This procedure was carried out using strips containing 39 kDa protein (GlpQ) from *B. hermsii* kindly supplied by Dr Tom Schwan (Rocky Mountain Laboratories, Hamilton, MT, US). Western blotting protocols were followed as described by Schwan and colleagues.[10]

Polymerase chain reaction (PCR) assay. Borrelia DNA was extracted from specimens using DNeasy Blood and Tissue Kits (Qiagen, Germany). DNA was amplified on Taqman real-time PCR using ABI Taqman 7500 (Applied Biosystems, US).[11,12]

The laboratory findings from all of these tests were reviewed and the diagnostic challenges and sample requirements were considered.

Results

During the study period, 19 of 100 patients tested for TBRF (19%) were shown to have evidence of infection with *B. hermsii* by a variety of methods, including dark field microscopy, Giemsa stain, serology (with or without western blotting), and PCR. Except for 2009 and 2014, at least one case of TBRF was identified in each year, with the top year being 2007 (seven cases). Most of the patients suspected to have TBRF (67%) were either young or middle-aged adults (20 to 60 years). Of the 19 patients with positive test results, 12 were female and 7 were male. Most of the positive cases were found in the Thompson-Okanagan region of British Columbia.

PCR assay and Giemsa stain testing using blood collected in an EDTA tube yielded the highest proportion of positive results (4 of 11 samples) followed by IgG IFA (19 of 109), IgM IFA (9 of 107), and dark field microscopy (2 of 14). The IgM and IgG western blot tests using GlpQ from *B. hermsii* supplied by Rocky Mountain Laboratories had the highest proportion of positive results, but the test strips have been unavailable since 2008. Later laboratory tests were limited to microscopy, IFA, and PCR only.

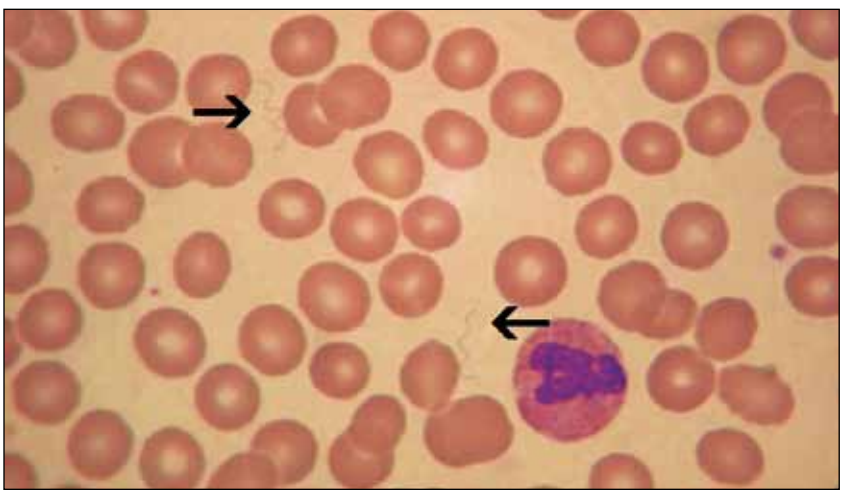

Figure 2. Tick-borne relapsing fever spirochetes (arrows) visible in a Giemsa-stained smear of peripheral blood.

Conclusions

The geographic distribution of blood samples found to be positive for *B. hermsii* during the review period is shown in Figure 3. The majority of cases of TBRF were actually identified in patients from the Kootenay-Boundary region, a known endemic region. The next largest group was from Greater Vancouver, a nonendemic region. Although we were unable to obtain travel histories for the majority of these patients, it is possible they visited an endemic region in the Pacific Northwest or Western US and then presented to a physician in a nonendemic region.[5] The percentage of TBRF cases in BC also seems high compared with other studies.[2]

Diagnostic challenges

Even though TBRF is one of the oldest tick-borne diseases reported in BC, the BCCDC Public Health Laboratory receives only 5 to 25 samples for testing each year and these are classic in nature. This indicates health care professionals may not be fully

aware of the presence of *B. hermsii* in BC.

Until laboratory results are available, tick-borne relapsing fever should be considered in patients with a history of recurrent fever and possible exposure to soft-bodied ticks. *O. hermsi*, the known vector for *B. hermsii,* feeds on a host for a short period ranging from 15 to 20 minutes. It often feeds at night and its bites are not painful or noticeable. This means hosts are usually bitten while asleep and remain unaware they have been bitten until symptoms of TBRF appear.[13] The innocuous feeding pattern of *O. hermsi* makes it important not to exclude TBRF from the differential diagnosis simply because there is no known history of tick bites.[14]

Physicians should be aware that the key symptom of TBRF is a sudden, high fever (39.2 °C or higher) that follows an incubation period of 7 days and lasts for 3 to 7 days.[5] Fever crises of less than 30 minutes are followed by diaphoresis, hypotension, and a decrease in temperature. Nonspecific symptoms may include chills, sweats, headaches, body aches, rash, nausea, vomiting, dry cough, neck pain, eye pain, confusion, and dizziness.[5,15,16] After an asymptomatic period that averages 7 days, an average of two relapsing episodes follow the first febrile episode.[17] General laboratory tests can provide evidence that supports a diagnosis of tick-borne relapsing fever. Patients with TBRF may present with mild leukocytosis, an elevated erythrocyte sedimentation rate and anemia, thrombocytopenia, elevated serum unconjugated bilirubin, elevated aminotransferase levels, prolonged prothrombin and partial thromboplastin times, proteinuria, and microhematuria. Patients with TBRF-associated myocarditis may present with a prolonged QT interval on electrocardiography. A patient with CNS Borrelia infection may exhibit moderate pleocytosis, mild-to-moderate elevated protein levels, and normal glucose levels.[15]

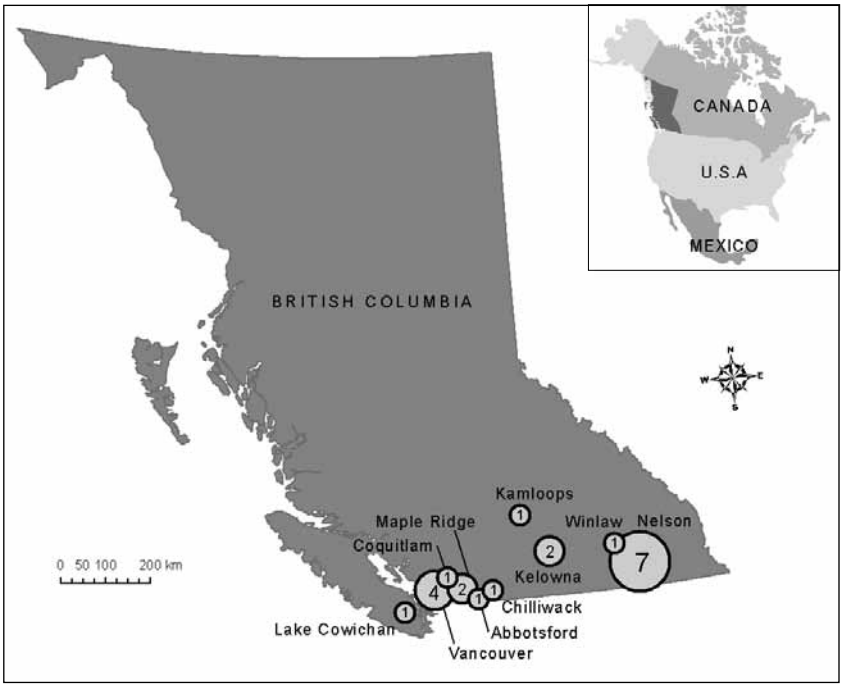

Figure 3. Geographic distribution of blood samples that tested positive for *B. hermsii* in British Columbia, 2006–2015.

While a significant number of samples were obtained from patients in the BC Lower Mainland, the patients were likely infected with tick-borne relapsing fever outside of this nonendemic region. (Note that three additional positive samples from the review period are not included on this map because of missing geographic information.)

Physicians should be aware that serological testing for *B. hermsii* can be affected by cross-reactivity with a related organism, *Borrelia burgdorferi*, which is well documented in the literature.[18,19] In this review, several of the 24 samples from 19 patients found to be positive for *B. hermsii* also tested positive in assays for *B. burgdorferi*. Positive *B. burgdorferi* results were found in 8 of 22 samples tested by enzyme immunoassay and 2 of 22 samples tested by IgM western blot. *B. burgdorferi* testing was not conducted for two patients because of sample quantity.

As well as being aware of cross-reactivity issues, physicians assessing patients for recurrent fever should consider general infections in the differential diagnosis, including salmonellosis, bartonellosis, tularemia, and Leptospira.[15,17] If there is a history of foreign travel, the differential diagnosis should also include amebic liver abscess, babesiosis, louse-borne relapsing fever, malaria, typhoid fever, and viral hepatitis. Depending on the patient history, a differential diagnosis may also include Colorado tick fever, ehrlichiosis, anaplasmosis, and rickettsiosis.

Blood sample requirements

When physicians suspect a patient experiencing recurrent fever is infected with *B. hermsii*, blood samples should be collected while the patient is

febrile and prior to antibiotic therapy. This is because culturing is often difficult and spirochete loads are highest during febrile periods. Documented cases of tick-borne relapsing fever have been missed in the past because blood was not drawn while the patient was febrile.[2] The appropriate samples are 7 mL of blood in a red-top serum separator tube for serology and 7 mL of blood in an EDTA tube for Giemsa staining and PCR. Blood samples can be submitted to the BCCDC Public Health Laboratory for Giemsa stain testing, *B. hermsii* serology/western blot testing, and PCR assay along with relevant clinical information. A convalescent specimen is required 2 to 4 weeks after collection of the first specimen.

Prior to 1998, isolates were established in pure culture after first inoculating laboratory mice (*Mus musculus*) with spirochetemic blood from the human patients. Starting in 1999, the BCCDC stopped using mouse amplification of *B. hermsii*.[3] Instead, infected human blood is now inoculated into BSK-H media and incubated at 34 °C with spirochetes being harvested and examined after two to four passages.[3] To note: *B. hermsii* strains were isolated using the mouse inoculation method (0.2 mL blood inoculated intraperitoneally) in laboratory mice followed by subsequent transfer to BSK II media; however, none of the culture results were positive for the period when animals were not used (data not shown).

Clinical management

Untreated *B. hermsii* infection can lead to sequelae. The infection has been shown to respond effectively to doxycycline/tetracycline, macrolides such as erythromycin, and penicillin, with effective treatment keeping mortality to less than 1%.[5,15,20] Although data suggest other agents are effective, including cephalosporins and chloramphenicol,[2,5,15] the ideal duration of therapy has not been established. Physicians should be aware that unlike an infection with the causative agent for louse-borne relapsing fever, *Borrelia recurrentis*, an infection with *B. hermsii* cannot be treated with a single dose of antibiotics. Current recommendations for treatment of *B. hermsii* TBRF require 7 days of oral or parenteral antibiotic therapy. Young children and pregnant women should be treated with erythromycin or penicillin.[15] Methods to protect against acquisition of TBRF include rodent-proofing buildings in endemic areas, avoiding rodent-infested buildings, and using DEET to protect against tick bites.[20,21]

Although this review did not identify patients with a posttreatment Jarisch-Herxheimer reaction, the reaction is common following the antibiotic treatment of spirochete infections, including syphilis,[22,23] leptospirosis,[24] TBRF, and non-TBRF Borrelia infections. Common signs and symptoms include fever, chills, rigors, diaphoresis, myalgia, increased heart rate, increased respiratory rate, and hypotension.[22] In rare cases, there may be cardiovascular collapse and death.[25,26] Approximately one-half of patients with TBRF will experience some sort of Jarisch-Herxheimer reaction and while this reaction can occur after antibiotic therapy[2,27,28] there is some question as to which antibiotics and doses of antibiotics are most associated with the Jarisch-Herxheimer reaction.[29-31] Mechanistically, this reaction occurs when a cytokine storm involving TNF, IL-6, and IL-8 follows the release of endotoxins from damaged and dying spirochetes.[25] Because this is an endotoxin-mediated process, symptoms occur within the first 4 hours after antibiotic therapy and will seem similar to a febrile crisis with rigors and a noticeable drop in blood pressure.[27] Patients should be watched closely for a Jarisch-Herxheimer reaction for 12 to 24 hours after antibiotic therapy in an environment where supportive care can be given.[9]

Summary

The identification and management of tick-borne relapsing fever caused by *B. hermsii* that have been transmitted by *O. hermsi* is important because the untreated illness can result in long-term sequelae. Tests conducted at the BCCDC Public Health Laboratory for this infection include dark field microscopy, immunofluorescence assay, western blot testing, and polymerase chain reaction assay. These tests require blood samples to be collected in a red-top serum separator tube and an EDTA tube, preferably while the patient is febrile and before antibiotic therapy is initiated. None of these tests is perfect and we believe that the gold standard for identifying *B. hermsii* TBRF cases includes an analysis of risk factors. Physicians should question patients about time spent in tents and cabins, whether patients have noticed insect bite marks after nights spent in forested areas, and whether they have traveled to an endemic region.[5,32]

By communicating about cases with the BCCDC and submitting appropriate samples for testing to the Public Health Laboratory, health care professionals can assist with determining the geographic range of *B. hermsii* and help monitor for expansion into regions of the province previously not known to harbor natural hosts and vectors of this spirochete. In future, molecular testing, an organized approach to diagnosis, and increased physician awareness of this illness should allow for more rapid and confident diagnoses and the

effective treatment of patients with *B. hermsii* TBRF.

Competing interests
None declared.

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