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Purple Paper

Lyme disease: a tick-transmitted bacterial disease of growing importance in Canada

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Key Points

- Lyme disease is a multi system disease that can be contracted in any Canadian province.
- Lyme disease is spreading in Canada and that spread can be expected to continue in the coming years.
- Studies to date have identified high risk endemic areas for Lyme disease within limited areas of Nova Scotia, New Brunswick, Quebec, Ontario, Manitoba and British Columbia.
- Current diagnostic tests are effective for detecting cases of disseminated, but not early, Lyme disease. Therefore, clinical cases of early Lyme disease are not well documented in Canada.
- Controversies exist over clinical and diagnostic aspects of Lyme disease but the 2006 guidelines published by the Infectious Disease Society of America have been strongly endorsed by an independent review panel.
- Research leading to improved diagnostics and to address medically unexplained symptoms is highly desirable.

Lyme Disease Activity in Canada

Early studies

Lyme disease is a tick-transmitted bacterial disease and one of many arthropod-transmitted zoonoses in Canada (Artsob, 2000). It is the most common tick-borne infection in the northern hemisphere. The only infecting species in North America currently known to cause Lyme disease is *Borrelia burgdorferi* sensu stricto whereas in Europe it may be caused by *B burgdorferi*, *B afzelii*, *B gairinii* and occasionally by other species of Borrelia (Steere, 2001).

In 1979, a biologist who had been working at Long Point, Ontario, a known site of *Ixodes scapularis* activity at that time (Watson & Anderson, 1976), started experiencing symptoms consistent with Lyme disease including swollen knees. His arthritic symptoms progressed over a 9 year period during which time *B burgdorferi,* the etiologic agent of Lyme disease, was demonstrated in *I dammini* (since reclassified as part of the *I scapularis* complex) ticks on Long point (Barker IK et al., 1992). Blood from this individual tested at the author's laboratory showed high antibody titres to *B burgdorferi* (unpublished observations). Antibiotic treatment was initiated with a successful outcome. Other early reports suggesting human cases of Lyme disease in Canada exist (Bollegraaf, 1988; Todd & Carter, 1989). However this may represent the earliest case of Lyme disease contracted in Canada known to meet the appropriate clinical, epidemiological and laboratory testing criteria to be considered a confirmed case.

Canadian studies to document the occurrence of *B burgdorferi* and Lyme disease in Canada were initiated in the 1980's with a primary focus on Ontario and British Columbia. An immunofluorescent antibody (IFA) serosurvey in 1985-86 of 200 Ontario patients with juvenile arthritis yielded only one individual with titres greater than 1:32. This patient did seroconvert during the course of her illness. However her arthritis was considered to be atypical for Lyme disease (Laxer & Artsob, 1988). Artsob et al (1993) examined sera from diagnostic submissions of 223 Ontario dogs with arthritic symptoms between 1987-1992 and found six dogs with significant IFA titres. Five of the six dogs had histories of travel to the United States while the sixth had been to Long

Point, the only known area of Lyme activity at that point in time.

Barker et al (1992) undertook an extensive study of small mammals and ticks at Long Point and 25 other localities throughout Ontario from 1987-1991 but could only find conclusive evidence for the occurrence of *B burgdorferi* at Long Point setting the stage for further studies over the next two decades. Banerjee and colleagues undertook similar studies on the west coast in the early 1990's demonstrating conclusively for the first time the presence of *B burgforferi* in British Columbia (Banerjee, 1993).

This early recognition of the expanding distribution of Lyme disease in the United States and the presence of *B burgdorferi* in established cycles within Canada prompted the Laboratory Centre for Disease Control, Health Canada and the Canadian Society of Infectious Diseases to cosponsor a Consensus Conference on Lyme Disease in January 1991 to address the epizootiology, epidemiology, clinical practice and laboratory aspects of Lyme disease (Anon., 1991). The published recommendations have served a very useful function as a guide to addressing Lyme disease in Canada but are outdated. The development of newer recommendations was initiated in 2006 at a national meeting in Toronto (http://www.phac-aspc.gc.ca/id-mi/lyme032006-eng.php) and this initiative is still in progress.

Updated studies

Studies over the past two decades have shown established cycles in Canada of the major Lyme disease tick vectors, *I scapularis*, the blacklegged tick (sometimes called the deer tick), and *I pacificus*, the western blacklegged tick. The cycle of enzootic transmission involves *B burgdorferi* circulating among vector larvae and nymphs and reservoir hosts. The strain of *B burgdorferi* in circulation may influence transmission dynamics and possibly the spectrum of human illness (Sperling & Sperling, 2009).

Surveillance in Canada has focused on identifying established populations of *Ixodes spp* to identify areas of potential human infection. For *I scapularis* surveillance, a passive approach of tick submissions has been implemented complemented by active surveillance in selected areas. Passive surveillance has shown us that ticks can be found in all 10 Canadian provinces, likely introduced in most instances by migrating birds (Ogden et al., 2006; Scott et al., 2010).

Active surveillance has demonstrated that the number of endemic areas in Canada has increased dramatically since the early 1990's to include several sites in southern Ontario, Nova Scotia, south-eastern and possibly southern Manitoba, one area in New Brunswick, parts of southern Quebec and in southern British Columbia (Ogden et al., 2009). A number of factors constrain the distribution of vector tick species including habitat suitability, host abundance, dispersal by hosts and climate (Ogden et al., 2008a). However it is clear that the relevant tick vectors for Lyme disease are spreading in Canada with increased risk for human infections to occur.

Lyme disease cases in Canada

The number of Lyme disease cases captured by the Canadian Public Health Agency's Notifiable Diseases Reporting System between 1994-2004 was 345 (http://www.phac-aspc.gc.ca/id-mi/lyme032006-eng.php). Lyme disease is notifiable in most provinces and has only recently become nationally notifiable. Approximately 150 cases have been reported in the last two years of which roughly half were travel-associated. Some people contrast the yearly number of Lyme disease cases reported in the United States (in the thousands) and Canada without apparently understanding that most of the cases reported in the United States are clinical cases based only on the presence of an erythema migrans (EM) rash. The diagnosis of clinical cases is suitable for clinicians to decide on case management but lacks specificity. These numbers are not currently captured in overall Canadian figures.

Lyme Disease Issues of Concern

Clinical

Lyme disease is a complex infection with a number of objective manifestations including a characteristic EM skin lesion (the most common presentation of early Lyme disease), certain neurologic and cardiac manifestations and pauciarticular arthritis (the most common presentation of late Lyme disease), all of which usually respond well to conventional antibiotic therapy (Feder, 2008; Ogden et al., 2008b;

Wormser et al., 2006). There are a small number of clinicians that describe a broader group of clinical manifestations for Lyme disease including a condition referred to as "chronic Lyme disease". They believe that patients have persistent *B burgdorferi* infection requiring long-term antibiotic treatment (Cameron et al., 2004). This view was challenged in a comprehensive review by Feder et al (2007) but remains a topic of considerable debate. Lyme disease guidelines were released by the Infectious Disease Society of America (IDSA) in 2006 (Wormser et el., 2006) and became highly politicized. They were the subject of an antitrust investigation by Connecticut Attorney General Richard Blumenthal following which a special independent review panel was carefully selected to review the guidelines. After multiple meetings, a public hearing, and extensive review of research and other information, the review panel concluded that the recommendations contained in the 2006 guidelines were medically and scientifically justified on the basis of all available evidence and that no changes to the guidelines were necessary (Lantos et al., 2010).

Laboratory

Laboratory testing for Lyme disease is of limited value for patients with early Lyme disease manifestations. Hence, clinicians observing patients with what they believe to EM rashes generally made a clinical diagnosis and initiate treatment. Laboratory testing becomes much more reliable when patients develop symptoms of disseminated Lyme disease and laboratory tests are recommended to support a clinical diagnosis. Serological tests are the primary tests of choice following a two tiered testing system of initial screening by ELISA with subsequent testing of ELISA positives by western blot (Canadian Public Health Laboratory Network, 2007). Polymerase chain reaction is generally not a recommended procedure but may be helpful for testing synovial or spinal fluid.

As with clinical diagnoses, certain controversies exist concerning laboratory testing. As noted, false negative test results can occur in patients with early Lyme who have not developed a sufficient immune response for antibody detection. In addition false positive test results can occur resulting in greater confidence in a positive serological test if a patient has a history of living in or visiting an endemic area. The CDC has published a caution about certain 'for profit' laboratories which utilize laboratory tests or interpretation criteria that have not been properly evaluated (Centres for Disease Control and Prevention, 2005).

It is generally conceded that the best ELISA screening test currently available utilizes a C6 peptide antigen consisting of a 26 amino acid sequence which represents the immunodominant portion of the *B burgdorferi* surface protein known as VlsE (Mogilyansky et al., 2004). This test detects antibodies to different Borrelia strains and may be better equipped to detect any antigenic variants of Borrelia that might arise and infect humans. Previously the National Microbiology Laboratory was the only lab in Canada to use the C6 ELISA on an experimental basis but the test became licensed in Canada in June, 2010 and is now available to be used as part of the Canadian diagnostic algorithm.

Final Comments

Lyme disease is a disease of increasing importance in Canada and the problem will only become worse in the coming years due to the influence of climate change. It is desirable to keep track and publicize any spread to reduce the risk of infection and alert physicians to anticipate the possibility of cases occurring within their practice area. Clinicians should also be aware of the low risk possibility of Lyme disease occurring in areas of Canada that extend beyond our currently defined established cycles.

The author believes that Canadian monitoring is very effective in detecting genuine cases of disseminated Lyme disease in this country but there is a void in our knowledge as to how many cases of Lyme disease are actually occurring since clinical case information is not captured well overall.

Controversies exist about certain clinical and diagnostic aspects of Lyme disease and there is clearly a need for better addressing medically unexplained symptoms which may be of infectious or non-infectious etiology. The development of improved sero- and non-serodiagnostic assays is also important e.g. the utilization of proteomic approaches to synthesize new antigen candidates. A

national and/or international effort to develop a serum repository from validated infections of different Borrelia species that infect humans would be invaluable to the development and validation of new assays.

The recent ruling of an independent panel upholding the 2006 IDSA guidelines is a victory for the mainstream medical community but clinicians will continue to encounter patients who self-diagnose or are guided to misinformation available from different websites. Canadian guidelines published in 1991 need updating, a slow process that is underway.

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