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Original article

Epidemiology of Lyme disease in low-incidence states☆,☆☆

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ABSTRACT

Lyme disease is the most common vector-borne disease in the U.S. Surveillance data from four states with a low-incidence of Lyme disease was evaluated. Most cases occurred after travel to high-incidence Lyme disease areas. Cases without travel-related exposure in low-incidence states differed epidemiologically; misdiagnosis may be common in these areas.

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1. Background

Lyme disease is a multi-system illness caused by the spirochete *Borrelia burgdorferi* with over 30,000 cases reported each year to CDC through the National Notifiable Diseases Surveillance System; the actual number of cases may be ten-fold higher (CDC, 2013; Hinckley et al., 2014). Over 95% of these cases occur in high-incidence states in the Northeast (Connecticut, Delaware, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia) and upper Midwest (Minnesota, Wisconsin) (CDC, 2015). However, cases of Lyme disease have been reported among residents of all 50 states. In the high-incidence states, the age distribution of cases with Lyme disease is typically bi-modal, with the highest incidence among children aged 5–9 years and adults aged 45–59; males account for 53% of all patients (Bacon et al., 2008). A retrospective analysis of surveillance cases was performed to explore the epidemiology of Lyme disease in low-incidence states.

2. Methods

Probable and confirmed cases[1] of Lyme disease reported during 2005–2009 from four states with a low-incidence of Lyme disease (Florida, South Carolina, Utah and Washington) were reviewed. Variables evaluated included age, sex, laboratory results, travel history, and clinical history. Laboratory evidence of infection was defined as positive laboratory results consistent with the two-tiered laboratory testing algorithm[2] for Lyme disease. In most

☆ Key Point: Most patients diagnosed with Lyme disease in low-incidence states report travel to high-incidence states. The epidemiology of Lyme disease in low-incidence states among patients who deny any travel-related exposure is distinct from that in high-incidence states. Accurate diagnosis of Lyme disease in low-incidence areas is essential to providing appropriate care.

☆☆ Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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[1] http://wwwn.cdc.gov/NNDSS/script/casedef.aspx?CondYrID=752&DatePub=1/1/2011%2012:00:00%20AM.
[2] http://www.cdc.gov/lyme/diagnosistesting/LabTest/TwoStep/.

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instances, health department employees obtained information on travel-related exposure when not documented in the case-report form. Travel-related exposure was defined as having been in a wooded, brushy, or grassy area (i.e., potential tick habitat) in a county, or state, where there is a high-incidence of reported Lyme disease (CDC, 2015). For cases with reported erythema migrans (EM), travel must have occurred within 30 days of development of the dermatologic lesion. State data were aggregated. Additional clinical information was utilized when available. Statistical evaluation of the data was performed using Epi Info™ version 7.1.1.14 (Centers for Disease Control and Prevention, Atlanta, GA). Comparisons were performed using Fisher's Exact tests where appropriate.

3. Results

During 2005–2009, a total of 385 confirmed and probable Lyme disease cases were reported to CDC from Florida, South Carolina, Utah and Washington. Median patient age was 44.5 years (range: 1–86 years), and 187 (49%) were male. Among 297 (77%) patients for whom a travel history was available, 250 (84%) had a history of recent travel to a high-incidence area (CDC, 2015) and 47 (16%) did not. Median age was similar for patients with and without travel-related exposure (46 years versus 41 years, respectively). However, the age distribution of patients with travel-related exposure was bi-modal, whereas the age distribution of patients without travel-related exposure was not (Fig. 1). Furthermore, 70% of patients without travel-related exposure were female, as compared with 43% of patients with travel-related exposure ($p < 0.0001$).

Among 285 patients with both clinical information about an EM and travel-history available, EM occurred as frequently in patients without travel-related exposure (31/47, 66%) as those with travel-related exposure (162/238, 68%; $p = 0.8$). Among patients with both clinical information and travel-history available, 24 (52%) of 46 patients without travel-related exposure reported musculoskeletal complaints as compared to 96 (40%) of 239 with travel-related exposure; this difference did not reach statistical significance ($p = 0.1$). Similarly, among the 261 patients with both clinical information about neurologic manifestations and travel-history available, the frequency of neurologic manifestations did not differ ($p = 0.2$) between the 4 (11%) of 35 without travel-related exposure and the 41 (18%) of 226 with travel-related exposure.

Among the 250 patients with travel-related exposure reported, 22 (9%) had no laboratory testing reported; 115 (45%) had insufficient laboratory evidence of infection. One hundred and thirteen (45%) cases had positive two-tiered testing including 47(19%) with positive EIA and IgM Wb, 65 (26%) with positive EIA and IgG Wb, and one (0.5%) case with CSF antibody titer greater than serum antibody titer. Among those with travel-related exposure who were tested, 87 (54%) of 162 cases with EM had a robust positive laboratory test.

Among 47 patients without travel-related exposure, 9 (19%) had no laboratory testing reported, 17 (36%) had insufficient laboratory evidence of infection. Twenty one (45%) had positive two-tiered testing results; 10 (21%), had a positive EIA and IgM Wb and 11 (23%) had a positive EIA and IgG Wb.

4. Discussion

Lyme disease is the most common vector-borne disease in the United States, and while the majority of cases are reported from the Northeast and upper Midwest, cases have been reported among residents of all states, including residents of states where infected vector ticks have not been identified. Diagnosed cases in these low-incidence areas could result from three potential scenarios: 1) true infection arising after travel to a high-incidence area, 2) locally-acquired infection arising from an unrecognized enzootic cycle, 3) or misdiagnosis.

Our analysis revealed that over 80% of cases in the low-incidence states studied were associated with recent travel to a high-incidence state. Notably, these cases had similar epidemiologic characteristics to cases from high-incidence states, with a slight male predominance and bi-modal age distribution (CDC, 2015). In contrast, cases in patients without travel-related exposure occurred predominantly among females aged 30–59 years; epidemiologic characteristics that are different than those expected

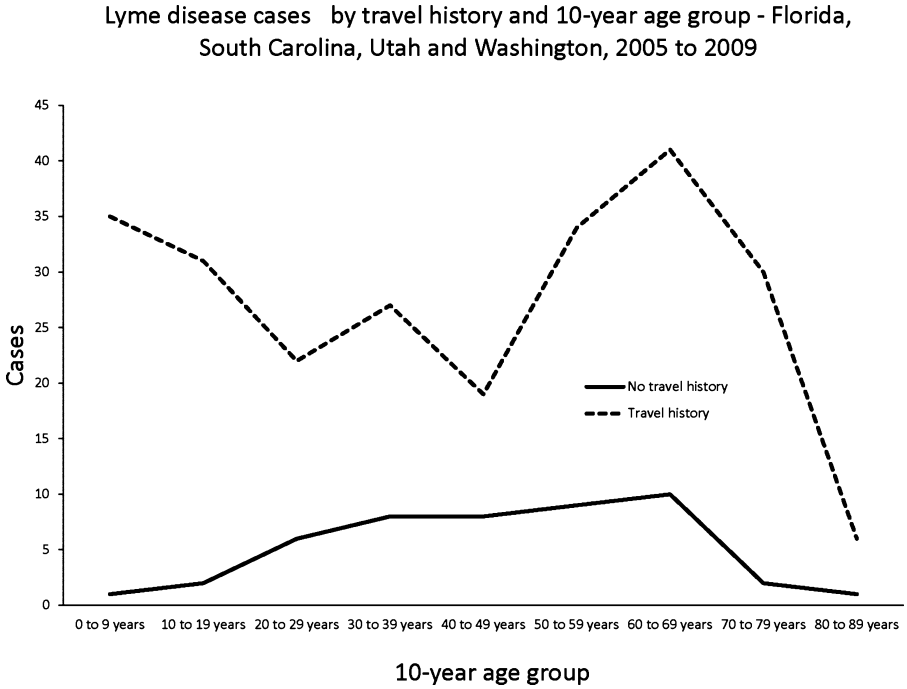

Fig. 1. Lyme disease cases by travel history and 10-year age group – Florida, South Carolina, Utah and Washington, 2005–2009. Dashed line represents cases with travel history, solid line represents cases without travel history.

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based on the epidemiology of Lyme disease patients as a whole (CDC, 2015).

While the diagnosis of patients with compatible clinical features and recent travel to high incidence areas is relatively straightforward, patients without a travel history pose a diagnostic dilemma for the health care provider in a low incidence area. The situation is complicated by the predictive value of both clinical features and laboratory testing in a low pre-test probability setting (Brett et al., 2014; Tugwell et al., 1997). In this setting, the negative predictive value of testing is quite high; if a patient's test is negative it almost certainly means that the patient does not have Lyme disease. Conversely, a positive test has a low predictive value, meaning that even patients with a suggestive skin lesion or positive serology may be misdiagnosed with Lyme disease. For example, our finding that 11 patients had two-tiered IgG EIA without travel-related exposure could easily represent false positive results; these would be expected given a test specificity of 99.5% and a sample of as few as 2200 patients (~110 patients tested per state per year). In the southeastern United States, southern tick associated rash illness (STARI), which is characterized by an erythema migrans-like rash but not caused by *B. burgdorferi*, also likely contributes to Lyme disease misdiagnoses (Wormser et al., 2005; Masters et al., 2008). Our finding that the epidemiologic features of non-travel associated cases from low-incidence states are unusual suggests that a substantial portion of these patients are misdiagnosed.

Prompt and appropriate treatment is desirable to securing a favorable clinical outcome in patients with Lyme disease (Wormser et al., 2006). However, the morbidity, mortality, healthcare expense and patient frustration associated with misdiagnosis mandate a thorough patient evaluation (Nelson et al., 2015; Brett et al., 2014; Patel et al., 2000; Sigal, 1996; Ettestad et al., 1995; Reid et al., 1998). The importance of obtaining a travel history cannot be overemphasized since it allows providers in low-incidence areas to recognize patients at higher risk of disease. Medical providers should perform an in-depth history and physical in any patient with suspected Lyme disease in low-incidence states, and be willing to investigate other etiologies for a patient's symptoms if testing is inconclusive, or if patients do not improve with treatment. Prior to unequivocal diagnosis of "locally-acquired" Lyme disease from a low-incidence area, clinicians should consider obtaining robust laboratory results for patients, including a seroconversion within two months of symptom onset or culture of the organism, in an accredited laboratory. Similarly, when evaluating surveillance data, cases detected in low-incidence areas do not necessarily correspond to endemic transmission of Lyme disease and should be evaluated carefully. Tests that have not been validated by the U.S. Food and Drug Administration should be avoided, as these may increase the chance for misdiagnosis (CDC, 2005).

An accurate diagnosis of Lyme disease is essential for patient health and appropriate utilization of healthcare resources regardless of the patient's state-of-residence. Most patients with Lyme disease in low-incidence states report recent travel to high-incidence Lyme disease states where they could have been exposed to infected ticks. Patients without this history of travel present a diagnostic dilemma; laboratory evidence of infection is important to securing a diagnosis, but the probability that a positive test result represents a true positive infection is lower in low-incidence areas. Clinicians and public health professionals should strongly consider the possibility of misdiagnosis of Lyme disease among patients without travel-related exposure in low-incidence states, helping ensure that patients with other illnesses are appropriately diagnosed and patients with true Lyme disease receive appropriate antibiotic therapy.

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