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BRIEF REPORT

Errors in Diagnostic Test Use and Interpretation Contribute to the High Number of Lyme Disease Referrals in a Low-Incidence State

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Lyme disease accounted for more than two-thirds (56 of 81, 69.1%) of all tick-borne disease referrals to a large, academic infectious diseases clinic in a low-incidence state. Deviations from diagnostic testing guidelines and errors in test interpretation were common (23 of 35, 65.7%), suggesting that frontline providers need additional clinical support.

Keywords. diagnostic testing; Lyme disease; referrals; tick-borne disease.

There were nearly 500 000 cases of tick-borne illness (TBI) reported to the Centers for Disease Control and Prevention (CDC) from 2004 to 2016, with Lyme disease accounting for 82% of cases [1]. More than 90% of Lyme disease cases are acquired between northern Virginia and New England. In contrast, North Carolina is considered a low-incidence state, consistent with the results of multiple clinical studies and entomological surveys [2–4]. Despite the low incidence, there is indirect evidence that provider and patient awareness of Lyme disease is increasing, resulting in increased care-seeking and testing. For example, since 2008, when the "probable" case classification was first introduced, the number of reported "confirmed" cases (eg, typical erythema migrans [EM] and laboratory evidence of infection and a known exposure to tick environment in a low-incidence state OR any case with ≥1 late manifestation with laboratory evidence of infection) in North Carolina has remained relatively constant while the number of probable cases increased >7-fold [5]. Therefore, we sought to quantify and describe the population of patients referred to a large academic infectious diseases (ID) clinic for TBI in a state with low incidence of Lyme disease.

METHODS

We performed a prospective review of all individuals referred to the University of North Carolina ID Clinic for evaluation of TBI (n = 1146). Clinic staff screened incoming referrals and flagged those potentially associated with TBI, including those referred for fever, arthritis/arthralgia, headache, rash, neurological symptoms, rash, fatigue, and "chronic Lyme," for review by study staff. We abstracted demographic information, clinical history, and laboratory test results from the available medical record and compared characteristics of the cohort using the Student *t* test for continuous variables and Pearson's chi-square or Fisher exact test for categorical variables. In a post hoc analysis, we categorized errors in diagnostic testing and test interpretation for the subset of patients referred for Lyme disease based upon deviations from established guidelines [6]. All data were collected in a REDCap database [7]. Statistical analyses were performed in Stata 12.1 (College Station, TX, USA). The study was approved by the institutional review board of the University of North Carolina at Chapel Hill.

RESULTS

From April 1, 2018, to March 31, 2019, we reviewed 81 referrals for tick-borne illness, representing 7.1% of all referrals to the clinic. The most common referring diagnosis was Lyme disease (56 of 81, 69.1%), while referrals for Rocky Mountain spotted fever (16 of 81, 19.8%) and ehrlichiosis (7 of 81, 8.6%) were less frequent. In addition, 1 patient was referred for babesiosis and another for "tick bite." The majority of referrals were from primary care providers, most of whom were not affiliated with our institution (Table 1). Nearly one-third of patients had been unsuccessfully referred to another academic ID clinic before our institution, and a significant number had previously been seen by another ID specialist.

The largest proportion of referred patients were middle-aged (median age [interquartile range {IQR}], 43.5 [33.0–54.5] years), Caucasian (39 of 45, 86.7%), and female (41 of 56, 73.2%). More than half (33 of 56, 58.9%) carried a comorbid psychiatric diagnosis, including 22 (39.3%) with depression, 19 (33.9%) with anxiety disorder, and 5 (8.9%) with post-traumatic stress disorder or histories of domestic abuse. Approximately 20% (11 of 56) of patients referred for Lyme disease were taking opioid medications for chronic pain, compared with only 4% (1 of 24) of patients referred for other tick-borne illnesses ($P = .07$). Fatigue and arthralgia were the most commonly listed symptoms, followed by

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Table 1. Provider and Patient Characteristics of Lyme Disease Referrals

Referring provider	
Medical specialty/setting, No. (%)	
Family medicine	27 (48.2)
Internal medicine	14 (25.0)
Urgent care	3 (5.4)
Neurology	3 (5.4)
Other	9 (16.1)
Provider qualifications, No. (%)	
Medical doctor	40 (72.7)
Physician assistant	8 (14.6)
Nurse practitioner	6 (10.9)
Practice affiliation, No. (%)	
Affiliated clinic	9 (16.1)
External clinic	47 (83.9)
Referred patient	
Demographic characteristics, No. (%)	
Median age, median (IQR), y	43.5 (33.0–54.5)
Female sex	41 (73.2)
Caucasian	39 (86.7)[a]
Resident of North Carolina	52 (92.9)
Insurance coverage, No. (%)	
Private insurance	29 (52.7)
Medicare	10 (18.2)
Medicaid	7 (12.7)
Uninsured	3 (5.5)
Other (eg, Tricare)	6 (10.9)
Chief complaint, No. (%)	
Fatigue	26 (46.4)
Arthralgia	26 (46.4)
Neurological symptoms	16 (28.6)
Rash	9 (16.1)
Fever	3 (5.4)
Previous care, No. (%)	
Referred to another ID clinic	17 (30.4)
Seen by another ID physician	9 (16.1)
Prior treatment, No. (%)	
Received antibiotics	34 (75.6)[b]
Received doxycycline	26 (78.8)
Duration, median (IQR), d	14 (14–21)
Multiple antibiotic courses	11 (29.7)

Abbreviations: ID, infectious diseases; IQR, interquartile range.

[a]Unable to determine race in 13 of 56 (23.2%).

[b]Unable to determine prior treatment in 11 of 56 (19.6%).

neurological symptoms. Most neurological symptoms were, however, atypical for Lyme disease, such as paresthesia, dizziness, and memory deficits, among others. Only 9 (16.1%) patients reported associated skin findings or rash. Five lesions were reported as blisters, bruising, eschar, folliculitis, or poison ivy, whereas no lesions were described as bullseye or targetoid in nature, and none were formally documented as EM.

Diagnostic test results, representing various combinations of enzyme immunoassay (EIA) and Western immunoblot (WB), were available for 34 of 56 (60.7%) patients. A total of 22 of 34 (64.7%) had an EIA performed, and of the 11 with a positive or equivocal result, all had a reflex WB. In contrast, 12 referrals (35.3%) only had WB testing performed. We also identified 3 patients who had results from commercial labs specializing in Lyme diagnostics (eg, IGeneX), but we did not use the alternative critieria to establish case classification.

About one-quarter (9 of 34, 26.5%) of initial tests were performed within 30 days of the onset of symptoms. One case was classified as confirmed (knee effusion positive for Lyme by polymerase chain reaction in an individual relocating from Pennsylvania), but had already received appropriate treatment and was being referred for post-treatment Lyme disease syndrome. Another had a positive EIA and IgM immunoblot result (ie, ≥2 bands present), but had not traveled, had no tick exposure, and the only symptoms were swelling of the wrists in the setting of pregnancy. Lastly, there was 1 patient with an IgM-positive WB result from 2017, who had been previously treated, who was being referred for chronic Lyme disease. All other referrals did not have supportive clinical or laboratory evidence to be classified as a case.

Of the 25 tests performed outside of the early period, the median time to the first test was >1 year after the onset of symptoms. A total of 15 (60%) had an EIA performed, 8 of which were positive or equivocal, whereas 10 had a WB performed in isolation, none of which were positive. We defined 3 referrals as confirmed cases, all of whom had recently resided or traveled to high-incidence states. One patient had a positive 2-tier result but no travel history or tick exposure, and her symptoms (eg, fatigue, memory loss) were not consistent with existing criteria. Thus, most patients (21 of 25, 81.0%) did not have compelling evidence of infection and were either inappropriately diagnosed or referred primarily for education and/or counseling.

We identified a large number of deviations from testing guidelines and errors in test interpretation. These included ordering an immunoblot without a preceding EIA (14 of 34, 41.2%), considering the presence of any bands on an immunoblot as a positive result (11 of 31, 35.5%), and interpreting a positive IgM immunoblot result as evidence of infection in the absence of a positive IgG result when outside the acute period (5 of 25, 20.0%). Overall, 23 of 35 (65.7%) of all referrals with evaluable test results demonstrated at least 1 error in diagnostic test ordering or interpretation.

Of the 45 patients for which treatment decisions were available, approximately three-quarters (34 of 45, 75.6%) received ≥1 course of antibiotics. Of note, all individuals reporting a rash, even if the description was not consistent with EM, received antibiotics. Doxycycline was the most frequently prescribed for a median duration (IQR) of 14 (14–21) days. At least 11 patients (29.7%) received multiple course of antibiotics, including 5 who had been taking various antibiotics for >1 year.

DISCUSSION

Despite relatively low incidence in North Carolina, Lyme disease is a frequent reason for referral to our ID clinic, accounting for more than two-thirds of all tick-related referrals. Most

patients did not have typical symptoms or diagnostic test results consistent with past or present Lyme infection and had already received an empirical course of treatment, findings similar to a report from a higher transmission area [8].

There are a number of reasons that may explain the disproportionate number of Lyme referrals compared with other endemic tick-borne illnesses. First, whereas infections with *Ehrlichia* and *Rickettsia* are common in North Carolina, these diseases typically present more acutely. Most patients are diagnosed and treated in primary care clinics and emergency departments without referral to an infectious diseases clinic [4]. Second, Lyme disease has received widespread attention in the popular media, driving patient demand for testing, treatment, and expert consultation [9]. Third, many clinicians are unfamiliar with current diagnostic and management guidelines, as evidenced by the high rates of diagnostic test misuse and misinterpretation. Fourth, many patients had Lyme testing performed as part of an evaluation for unexplained symptoms and may simply have wanted additional specialist input.

Based on these findings, we believe there are concrete changes that can be made to diagnostic testing interfaces to reduce errors in test interpretation and minimize misdiagnosis, which can sow confusion and distrust of the medical profession. First, immunoblot testing should only be available in response to a positive or indeterminate enzyme-linked immunoassay result. Although this is clearly outlined in current guidelines, providers, and especially those using commercial laboratories, frequently ordered an immunoblot in isolation. Recently approved changes in the 2-step serologic testing algorithm could diminish use of the immunoblot in favor of sequential EIAs, which may reduce confusion in interpreting results [10]. Second, we would recommend that, given the poor specificity, laboratories not routinely perform IgM immunoblot testing when symptoms have been present for >30 days [11, 12]. Lastly, there is a clear need for ongoing educational and decision-making support among frontline providers, especially as the Infectious Diseases Society of America prepares to release updated guidelines for the diagnosis and management of Lyme disease. These programs should emphasize recommendations such as only testing patients with specific neurological symptoms (eg, meningitis, radiculoneuritis, and cranial neuropathies) and not recommending additional antibiotics in patients with persistent or recurring nonspecific symptoms, as these issues were key drivers of our incoming referrals.

Our review is limited by not having access to the complete medical record in most cases, only the records accompanying the referral. We may also have underestimated the total number of TBI-related referrals if they were not associated with diagnoses specific to tick-borne disease (eg, neutropenia). Finally, our principal finding, that a high rate of errors in diagnostic test interpretation should not be generalized to reflect general practice patterns within the community, provides insight into potential drivers of referrals.

In summary, we found that pervasive concern about Lyme disease, despite low endemicity, drove referrals to our ID clinic. Confusion regarding interpretation and recommended use of diagnostic testing was prevalent among the referrals we reviewed. These results underscore the need for clear guidelines for testing and treatment, as well as improvement in the way the test results are displayed. Until better diagnostics for tick-borne illness are developed, these measures will support frontline clinicians struggling to respond to these often marginalized patients seeking explanations for nonspecific symptoms such as chronic pain and fatigue.

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References

1. Rosenberg R, Lindsey NP, Fischer M, et al. Vital signs: trends in reported vectorborne disease cases - United States and territories, 2004–2016. MMWR Morb Mortal Wkly Rep **2018**; 67:496–501.
2. Diuk-Wasser MA, Hoen AG, Cislo P, et al. Human risk of infection with *Borrelia burgdorferi*, the Lyme disease agent, in Eastern United States. Am J Trop Med Hyg **2012**; 86:320–7.
3. Wallace JW, Nicholson WL, Perniciaro JL, et al. Incident tick-borne infections in a cohort of North Carolina outdoor workers. Vector Borne Zoonotic Dis **2016**; 16:302–8.
4. Boyce RM, Sanfilippo AM, Boulos JM, et al. *Ehrlichia* infections, North Carolina, USA, 2016. Emerg Infect Dis **2018**; 24:2087–90.
5. North Carolina Department of Health and Human Services: Division of Public Health. Annual update on surveillance for Lyme disease in North Carolina. Available at: http://epi.publichealth.nc.gov/cd/lyme/docs/Lyme_memo_2017.pdf. Accessed 21 November 2019.
6. Centers for Disease Control and Prevention. Recommendations for test performance and interpretation from the Second National Conference on Serologic Diagnosis of Lyme Disease. MMWR Morb Mortal Wkly Rep **1995**; 44:590–1.
7. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform **2009**; 42:377–81.
8. Kobayashi T, Higgins Y, Samuels R, et al. Misdiagnosis of Lyme disease with unnecessary antimicrobial treatment characterizes patients referred to an academic infectious diseases clinic. Open Forum Infect Dis **2019**; 6(X):XXX–XX.
9. Lantos PM. Chronic Lyme disease. Infect Dis Clin North Am **2015**; 29:325–40.
10. Mead P, Petersen J, Hinckley A. Updated CDC recommendation for serologic diagnosis of Lyme disease. MMWR Morb Mortal Wkly Rep **2019**; 68:703.
11. Lantos PM, Lipsett SC, Nigrovic LE. False positive Lyme disease IgM immunoblots in children. J Pediatr **2016**; 174:267–9.e1.
12. Seriburi V, Ndukwe N, Chang Z, et al. High frequency of false positive IgM immunoblots for *Borrelia burgdorferi* in clinical practice. Clin Microbiol Infect **2012**; 18:1236–40.