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Short communication

A minority of children diagnosed with Lyme disease recall a preceding tick bite

Lise E. Nigrovic[a,*], Desiree N. Neville[b], Fran Balamuth[c], Jonathan E. Bennett[d], Michael N. Levas[e], Aris C. Garro[f], for Pedi Lyme Net

[a] Division of Emergency Medicine, Boston Children's Hospital, Boston, MA, United States
[b] Division of Emergency Medicine, Children's Hospital of Pittsburgh, Pittsburgh, PA, United States
[c] Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, United States
[d] Division of Emergency Medicine, A.I. Dupont Hospital for Children, Wilmington, DE, United States
[e] Pediatric Emergency Medicine, Medical College of Wisconsin, Milwaukee, WI, United States
[f] Division of Emergency Medicine, Rhode Island Hospital, Providence, RI, United States

A B S T R A C T

Of 1770 children undergoing emergency department evaluation for Lyme disease, 362 (20.5%) children had Lyme disease. Of those with an available tick bite history, only a minority of those with Lyme disease had a recognized tick bite (60/325; 18.5%, 95% confidence interval 14.6–23.0%). Lack of a tick bite history does not reliably exclude Lyme disease.

1. Introduction

A single dose of doxycycline within 72 h of a recognized *Ixodes scapularis* tick bite reduces the risk of later developing Lyme disease (Nadelman et al., 2001; Warshafsky et al., 2010), but requires timely recognition that a tick bite has occurred. To determine the potential of post-exposure antibiotic prophylaxis as a Lyme disease prevention strategy, we explored whether children with Lyme disease or their caregivers recalled a preceding tick bite. To this end, we assembled a prospective cohort of children undergoing emergency department (ED) evaluation for Lyme disease. Specifically, we determined the proportion of children diagnosed with Lyme disease who had a recognized tick bite and then compared this proportion between children with and without a diagnosis of Lyme disease.

2. Materials and methods

We performed a prospective study of children aged 1–21 years who presented to one of six EDs each located in a Lyme disease endemic area participating in Pedi Lyme Net who underwent acute evaluation for Lyme disease between May 2015 and September 2018 (Nigrovic et al., 2017). The institutional review board of each participating center approved the protocol with permission for data sharing.

Study staff identified eligible patients and approached parents or legal guardians (patient age 1–17 years) and patients (age 18–21 years) to obtain written informed consent. For enrolled children, we collected clinical phenotype as well as a research biosample. Treating clinicians asked enrolled children and their parents or caregivers whether a tick bite had been recognized within the year prior to ED evaluation (time period selected based to maximize recall). For those children with a recognized tick bite, we determined the time since the tick bite occurred (in weeks). We performed telephone follow-up one-month form the time of enrollment.

Using a research serum sample, we obtained the commercially-available C6 enzyme immunoassay (EIA) licensed by Oxford Immutec, Ltd. (Marlborough, MA) performed in a single research laboratory (Branda Laboratory, Massachusetts General Hospital; Boston, MA). Children with positive or equivocal C6 EIA tests had an immunoblot performed and interpreted using standardized criteria (Centers for Disease Control and Prevention (CDC), 1995). Any positive IgG or a positive IgM alone with < 30 days of symptoms were classified as a positive immunoblot. We defined a case of Lyme disease with a physician diagnosed erythema migrans (EM) lesion or a positive or equivocal C6 EIA followed by a positive immunoblot. We defined Lyme disease stage as follows: early (EM lesion), early-disseminated (multiple EM, cranial neuritis, meningitis, carditis) and late (arthritis).

Our primary goal was to report the frequency of a known tick bite in children with Lyme disease overall and by stage. Our secondary goal was to compare the frequency of known tick bites between children with and without Lyme disease in cohort of children undergoing ED

* Corresponding author at: Division of Emergency Medicine, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA, 02115, United States.
E-mail address: Lise.nigrovic@childrens.harvard.edu (L.E. Nigrovic).

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evaluation for Lyme disease. We used Chi Square test to compare proportions.

We used SPSS version 24.0.0 for all analyses (IBM SPSS Statistics, IBM Corporation; Armonk, NY).

3. Results

Over the study period, we enrolled 1770 children with successful research biosample collection. Each of the six participating sites enrolled between 70 and 439 eligible study patients. The median age of participants was 9 years [interquartile range (IQR) 5–13 years] and 993 (56.1%) were male. Overall, 362 children (20.5% of study population) had Lyme disease.

Of the 1770 study patients, treating clinicians obtained a tick bite history for 1587 children (89.7% of those enrolled). Of those, 167 had a known tick bite (10.5% with available tick bite history) which occurred a median of 4 weeks prior to evaluation (IQR 1–8 weeks). Of the 325 children with Lyme disease and an available tick bite history, only a minority had a recognized tick bite [n = 60; 18.5%, 95% confidence interval (CI) 14.6–23.0%]. More children younger than 8 years of age had a recognized tick bite (< 8 years 85/653; 13.0%, 95% CI 10.7–15.8% vs. > = 8 years of age 82/934; 8.8%, 95% CI 7.1–10.8%; difference 4.2%, 95% CI 1.2–7.5%).

A history of a tick bite was more frequent in children with Lyme disease (59/298, 19.8% of children with Lyme disease vs. 98/1139, 8.6% of those without Lyme disease; difference 11.2%, 95% CI 6.7–16.3%; Table 1). More children with EM lesions recalled a preceding tick bite than those with early-disseminated or late Lyme disease.

4. Discussion

In our prospective cohort of children undergoing ED evaluation for Lyme disease, most children had symptoms of early-disseminated or late (i.e. arthritis) infection. Approximately one in five children with Lyme disease had a recognized tick bite within the past year. Younger children and those with an EM lesion were more likely to recall a recent tick bite. We demonstrate that lack of tick bite history does not reliably exclude the possibility of Lyme disease for children from endemic areas.

In endemic areas, *Ixodes* tick species transit Lyme disease as well as other tick-borne infections and co-infections. In a post-exposure antibiotic prevention trial of 387 children and adults with an *Ixodes* tick bite attached between one and three days, a ten day course of amoxicillin did not prevent Lyme disease [0/192 (0%) amoxicillin vs. 2/173 placebo (1.2%); p = 0.22) (Paules et al., 2018). However, this trial was potentially underpowered to detect a clinically significant effect. In a second trial of 482 adults with an *Ixodes* tick bite with an one to three days of tick engorgement, a single dose of doxycycline prevented Lyme disease [1/235 (0.4%) doxycycline vs. 8/247 (3.2%) placebo developed a single EM lesion; p = 0.04] (Nadelman et al., 2001). Similarly, in a meta-analysis of four trials doxycycline reduced risk of developing Lyme disease (2.2% placebo vs. 0.2% single-dose doxycycline; pooled odds ratio 0.084, 95% CI 0.002-0.57) (Warshafsky et al., 2010).

Although the actual risk of developing Lyme disease after a single tick bite was quite low, even in endemic areas, clinicians should consider post-exposure doxycycline to prevent Lyme disease for patients with a recognized tick bite. Recent data demonstrate that short-courses of doxycycline did not demonstrate cosmetically significant dental staining (Todd et al., 2015), suggesting that a single dose of doxycycline may be safe, even for the youngest children. However, as post-exposure antibiotic prophylaxis requires timely tick bite recognition, our findings suggest that wide-spread implementation of this prevention strategy is unlikely to prevent most cases of Lyme disease in children.

Our study has several limitations. First, we relied on the treating clinician to record the history of a recognized tick bite after obtaining a history from a patient and their caregivers. Importantly, this history was recorded before Lyme disease test results were available, reducing the potential for bias. Second, we did not collect the duration of tick attachment, as parents frequently did not recall or were unaware of this timing. Third, Lyme disease tests can be falsely negative early in disease (Steere et al., 2008) and we did not routinely perform convalescent Lyme disease testing for children with initially negative test results. Fourth, although positive Lyme disease serology may represent past rather than active infection, the background seropositive rate at the six participating centers was lower than that reported in adults (1.6%) (Garro et al., 2018). Fifth, our study was not designed to determine the risk of developing Lyme disease after a recognized tick bite. Last, as each participating ED was located in a Lyme disease endemic area, our findings may not be applicable to regions with lower Lyme disease incidence or the primary care setting.

5. Conclusions

More than 300,000 new cases of Lyme disease are diagnosed each year in the United States,(Hinckley et al., 2014) with approximately half of new cases occurring in children. Prevention strategies are needed to reduce the burden of tick-borne illnesses, including Lyme disease. Although a history of a recognized tick bite increases the risk of child having Lyme disease, most children who develop Lyme disease are not aware of a preceding bite. Therefore, absence of a tick bite history does not reliably exclude the possibility a child might have Lyme disease. In addition, post-exposure antibiotic prophylaxis may have only a small impact on preventing new Lyme disease cases. Alternate prevention strategies such as exposure reduction (protective clothing or repellants) (Eisen and Dolan, 2016) as well as a safe and effective Lyme disease vaccine (Nigrovic and Thompson, 2007) should be priority areas for investigation.

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Table 1
History of known tick bite for children with and without Lyme disease.

	N	Known tick bite n = 157 n (%)	No known tick bite n = 1,280 n (%)	Difference % (95% CI)
Lyme disease	325	60 (18.5%)	265 (81.5%)	63.1% (56.6, 68.5)
Early	34	13 (38.2%)	21 (61.8%)	23.5% (0, 43.8)
Early-disseminated	103	20 (19.4%)	83 (80.6%)	61.2% (48.9, 70.3)
Late	188	27 (14.4%)	161 (85.6%)	71.3% (63.2, 77.4)
Not Lyme disease	1262	107 (8.5%)	1155 (91.5%)	83.0% (80.7, 85.0)

Conflicts of interest

None.

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