Risk Factors for Clinician-Diagnosed Lyme Arthritis, Facial Palsy, Carditis, and Meningitis in Patients From High-Incidence States

Natalie A. Kwit,1 Christina A. Nelson,1 Ryan Max,1 and Paul S. Mead1
1Centers for Disease Control and Prevention, Fort Collins, Colorado

Background. Clinical features of Lyme disease (LD) range from localized skin lesions to serious disseminated disease. Information on risk factors for Lyme arthritis, facial palsy, carditis, and meningitis is limited but could facilitate disease recognition and elucidate pathophysiology.

Methods. Patients from high-incidence states treated for LD during 2005–2014 were identified in a nationwide insurance claims database using the International Classification of Diseases, Ninth Revision code for LD (088.81), antibiotic treatment history, and clinically compatible codiagnosis codes for LD manifestations.

Results. Among 88,022 unique patients diagnosed with LD, 5,122 (5.8%) patients with 5,333 codiagnoses were identified: 2,440 (2.8%) arthritis, 1,853 (2.1%) facial palsy, 534 (0.6%) carditis, and 506 (0.6%) meningitis. Patients with disseminated LD had lower median age (35 vs 42 years) and higher male proportion (61% vs 50%) than nondisseminated LD. Greatest differential risks included arthritis in males aged 10–14 years (odds ratio [OR], 3.5; 95% confidence interval [CI], 3.0–4.2), facial palsy (OR, 2.1; 95% CI, 1.6–2.7) and carditis (OR, 2.4; 95% CI, 1.6–3.6) in males aged 20–24 years, and meningitis in females aged 10–14 years (OR, 3.4; 95% CI, 2.1–5.5) compared to the 55–59 year referent age group. Males aged 15–29 years had the highest risk for complete heart block, a potentially fatal condition.

Conclusions. The risk and manifestations of disseminated LD vary by age and sex. Provider education regarding at-risk populations and additional investigations into pathophysiology could enhance early case recognition and improve patient management.

Keywords. claims analysis; disseminated Lyme disease; epidemiology; Lyme disease; tick-borne disease.

Each year, an estimated 300,000 Americans are diagnosed with Lyme disease (LD), a zoonotic infection transmitted by certain species of Ixodes ticks caused by Borrelia burgdorferi and the newly identified Borrelia mayonii [1–3]. In 2015, 95% of confirmed LD cases were reported from 14 states, concentrated heavily in the Northeast, mid-Atlantic, and upper Midwest [4]. Incidence is highest among boys aged 5–9 years, followed by men aged 45–59 [5, 6].

Patients with early LD typically present with a localized skin lesion known as erythema migrans (EM) and constitutional symptoms such as fever, chills, and headache. Because B burgdorferi is tropic to cardiac, nerve, and joint tissue, untreated infection can progress to more serious disseminated disease including carditis, meningitis, facial palsy, and arthritis [7]. It is unknown, however, why certain patients develop cardiac infection whereas others manifest nerve or joint symptoms. Distinct B burgdorferi subtypes have been associated with spirochtemia and disseminated disease [8], and geographically distinct strain lineages vary in virulence and inflammatory potential [9]. Gender disparity between cutaneous and noncutaneous manifestations of LD has been reported in Europe where multiple genospecies cause LD [10]. In the United States, Lyme carditis has been shown to be more common among young adult males [11], but additional information on risk factors for these LD manifestations is limited.

National surveillance provides useful descriptions of LD epidemiology; however, clinical characteristics are reported voluntarily and subject to selection bias depending on reporting modality (ie, active vs passive surveillance) [12]. Variability in surveillance practices between states also limits interpretation of reported clinical data.

Medical claims data are an additional source of LD epidemiologic information that offer several advantages such as large sample size, robust capture of the full continuum of care, and inclusion of detailed prescription drug information [13]. Overall trends in the age, sex, and geographic distribution of persons with LD in medical claims databases have been found to be similar to those seen in US surveillance data [1].

Information on risk factors for these serious forms of LD could promote early recognition of disseminated LD among...
identified risk groups and improve understanding of the pathophysiology of various forms of LD. The objective of this study was to characterize populations at increased risk for specific manifestations of disseminated LD using information from a large, nationwide medical claims database.

METHODS

Medical Claims Database
The Truven Health MarketScan Commercial Claims and Encounters databases contain diagnosis and treatment information for ~40 million employer-insured Americans and their dependents per year. The databases include patients <65 years old from all 50 states. Deidentified data on enrollee demographics, inpatient and outpatient medical visits, and prescription drugs is available. Results of ordered laboratory tests are not available. Each patient encounter was coded by a clinician or billing specialist according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Inpatient admissions included 1 principal diagnostic code and up to 14 secondary diagnostic codes that represent the final summary of discharge diagnoses billed to insurance. Outpatient encounters included up to 4 diagnostic codes but did not differentiate between principal and secondary diagnoses.

Inclusion Criteria
The study population was defined as patients from high-incidence areas diagnosed with LD during 2005–2014 while enrolled in a participating health insurance plan for the entirety of at least 1 calendar year. High-incidence areas were defined as the 14 states from which 95% of LD cases were reported to the Centers for Disease Control and Prevention (CDC) in 2015 [4], plus the District of Columbia. Records were identified using the ICD-9-CM code for LD (088.81). Detailed inclusion criteria were described by Nelson et al [1]. Inpatient encounters were restricted to those with 088.81 as the principal diagnosis or 088.81 as a secondary diagnosis along with a principal diagnosis code for a known manifestation of LD or credible coinfection (Appendix). Outpatient encounters were restricted to those with the 088.81 ICD-9-CM code plus an antimicrobial prescription of at least 7 days’ duration filled within 30 days of the visit date. Antimicrobial drugs were limited to those commonly recommended for the treatment of LD and 3 additional closely related or known historical antimicrobial treatments (Appendix) [14]. The initial visit that met the inclusion criteria within the study period was considered the date of the event. Only the inpatient admission was included when both an inpatient and outpatient event occurred within the same year.

Patients with disseminated LD were defined as those who met the inclusion criteria above and had a clinically compatible codiagnosis code(s) for infectious arthritis, facial palsy, carditis, or meningitis within 30 days of the date of LD diagnosis. Patients with Lyme arthritis were identified using codes for pyogenic arthritis (711.0x), arthropathy associated with other bacterial disease (711.4), unspecified infective arthritis (711.9), unspecified monoarthritis (716.6x), and joint effusion (719.0x). The ICD-9-CM diagnosis codes used to identify patients with facial palsy due to LD included Bell’s palsy (351.0), other/unspecified facial nerve disorder (351.8 and 351.9), facial weakness (781.94), injury to facial nerve (951.4), injury to other specified cranial nerves (951.8), and injury to unspecified cranial nerve (951.9). Patients with Lyme carditis were identified using ICD-9-CM codiagnosis codes for acute pericarditis—unspecified or in diseases classified elsewhere (420.xx), myocarditis—unspecified or in diseases classified elsewhere (422.xx, 429.0), and conduction disorders (426.0–426.6x, 426.89, and 426.9). Patients with Lyme carditis were subcategorized into those with conduction disorders and further differentiated to those with third-degree (ie, complete) atrioventricular block (426.0) to compare these patients within the carditis group. Patients were considered to have Lyme meningitis if the record also included an ICD-9-CM code for meningitis in other bacterial diseases (320.7), meningitis due to Gram-negative bacteria, not elsewhere classified (320.82), nonpyogenic meningitis (322.0), meningitis, unspecified (322.9), or meningitis due to other/unspecified bacteria (320.89 and 320.9). All other patients without one of the codiagnoses listed above were considered to have nondisseminated LD.

Statistical Methods
We calculated descriptive and analytic statistics using JMP software version 11 (SAS Institute, Cary, NC). Because disseminated LD is relatively rare, odds ratios (ORs) were used to approximate risk ratios, or level of increased risk. We used logistic regression to compute ORs and associated 95% confidence intervals (CIs) adjusted for multiple comparisons. For simplicity of comparison, age was grouped into 5-year categories. The 55–59 year age category was used as the referent group for all ORs to allow clear comparisons across groups. The denominator for incidence rate calculations was derived from the total MarketScan population enrolled for at least 1 entire year within the study period.

RESULTS

Study Population
A total of 88,022 unique patients from high-incidence states diagnosed with LD were identified in the MarketScan databases among 217,389,868 person-years of observation from 2005 to 2014. Average annual incidence of LD within the MarketScan population was 40.5 per 100,000 persons. Median patient age was 41 years; 51% were male. A total of 5,122 (5.8%) patients with 5,333 disseminated LD codiagnoses were identified: 2,440 (2.8%) arthritis, 1,853 (2.1%) facial palsy, 534 (0.6%) carditis, and 506 (0.6%) meningitis codiagnoses (Table 1). Incidence of each manifestation among the MarketScan population during
the study period was 1.1, 0.9, 0.2, and 0.2 per 100,000 persons, respectively. A total of 208 (0.24%) patients had more than 1 disseminated codiagnosis; meningitis and facial palsy codiagnosis was the most common (n = 148; 0.17%).

Epidemiology of Disseminated Lyme Disease Manifestations

Patients with disseminated LD had a lower median age (35 vs 42 years) and higher male proportion (61% vs 50%) than patients with nondisseminated LD. When comparing specific manifestations, patients with arthritis had the lowest median age, followed by meningitis, facial palsy, and carditis patients (Table 1). The highest proportion of males (71%) was among carditis patients, and an even higher proportion of patients with third-degree (complete) heart block (121 of 148; 82%) were male. Patients with arthritis had the next highest proportion of males (62%).

Overall, 18.4% of patients with disseminated LD were hospitalized compared with <1% of patients without disseminated LD. The majority of patients with meningitis (366 of 506; 72.3%) and half of patients with carditis (267 of 534; 50%) were hospitalized, whereas only 14.3% and 8.4% of patients with facial palsy and arthritis were hospitalized, respectively (Table 1).

The highest proportion of nondisseminated LD cases were diagnosed in July (21.1%) and June (20.7%), followed by August (11.6%), and May (9.4%). Patients with disseminated LD were diagnosed slightly later than patients with nondisseminated LD; most were diagnosed in July (21.5%), followed by August (14.0%), June (13.2%), then October (8.7%). When each specific manifestation of disseminated LD was analyzed by month of diagnosis, a similar lag was seen for each manifestation, although arthritis was more diffuse and peaked later (Figure 1).

Risk Factors for Specific Disseminated Lyme Disease Manifestations

Incidence of Lyme arthritis for all male age groups exceeded that of females, but it was highest among 5- to 14-year-olds (Figure 2A). When evaluated for risk, children aged 0–14 years were disproportionately affected. Both male (OR, 3.5; 95% CI, 3.0–4.2) and female (OR, 2.5; 95% CI, 2.0–3.1) patients aged 10–14 years had the highest risk of arthritis, relative to the 55- to 59-year-old reference group (Figure 2B). Increased risk of arthritis persisted longer in males, up to 19 years.

The incidence of facial palsy was highest among males aged 10–14 years (Figure 2C). Males aged 5–29 years had significantly elevated risk of facial palsy compared to 55- to 59-year-olds, but those aged 20–24 years (OR, 2.1; 95% CI, 1.6–2.7) and 15–19 years (OR, 2.1; 95% CI, 1.6–2.6) had the greatest risk (Figure 2D). The only age group among females with an increased risk for facial palsy compared to the referent group was 10–14 years (OR, 1.6; 95% CI, 1.2–2.1).

Compared to females, incidence of Lyme carditis was greater for males of every age group except the 0- to 4-year-olds, and it was highest among males aged 60–64 and 20–24 years (Figure 2E). Males aged 20–24 years had a substantially higher risk of Lyme carditis than other age and sex groups (OR, 1.8; 95% CI, 1.2–2.9), followed by males aged 30–44 and 60–64 years (Figure 2F).

Incidence of meningitis was highest for males aged 5–9 years and females aged 10–14 years (Figure 2G). Females aged 10–14 years had the highest risk for Lyme meningitis (OR, 3.4; 95% CI, 2.1–5.5), followed by males aged 20–24 years (OR, 3.1; 95% CI, 1.9–5.1), but females aged 5–9 and males aged 5–19, 30–34, and 45–49 years also had a significantly elevated risk of meningitis compared to the referent group (Figure 2H).

Risk Factors for Complete Heart Block Due to Lyme Carditis

When carditis patients were subcategorized into those with third-degree (complete) atrioventricular block, incidence was highest among 60- to 64-year-old and 15- to 19-year-old males (Figure 3A). Males aged 15–19 (OR, 3.1; 95% CI, 1.6–6.4) and 25–29 years (OR, 3.0; 95% CI, 1.3–7.1) had the highest risk for complete heart block, although these groups did not have a statistically significant increased risk for Lyme carditis overall (Figure 3B). Elevated risk for carditis and third-degree atrioventricular block was not identified among any female age groups.

DISCUSSION

In the United States, overall characteristics of patients with LD are well defined, but information on the epidemiology of
specific clinical manifestations is limited. Through this study, we identified patient characteristics associated with specific manifestations of disseminated LD. Most notably, risk of carditis and facial palsy was highest among young men; meningitis and arthritis affected children and adolescents of both sexes, extending to a higher age among males. Patients with these LD manifestations tended to be hospitalized, underscoring the severity of illness and need for early recognition of disease.

In this study, patients with Lyme arthritis were more likely to be aged 0–14 years of either sex. Lyme arthritis was originally observed in a Connecticut population with a median age of 11 years [15]. In Lyme-endemic areas, up to 50% of pediatric monoarticular arthritis and 5% of pediatric hip arthritis is caused by LD [16, 17]. Because symptoms of Lyme arthritis can appear days to months after infection, it is diagnosed throughout the year [6]. In a prospective cohort study, children with LD were more likely to present with fever and arthritis and less likely to present with EM compared to adults [18]. It is interesting to note that the increased risk of arthritis extended to an older age group in males, up to 15–19 years, but not in this age group for females. Although additional research is warranted, one potential hypothesis for this finding is that *B. burgdorferi* has a physiological affinity for growing bones and joints, and the delayed age of peak growth and higher peak height velocity in boys versus girls might explain sex differences in risk of Lyme arthritis in this age group [19].

Physiologic cardiac stress and spirochetal and host genetic factors might also play a role in Lyme carditis risk. In a study of cardiac autopsy specimens from 5 patients with sudden cardiac death due to Lyme carditis, 80% were male and median age was 28 years [25]. In these patients, *B. burgdorferi* spirochetes were observed to colocalize with decorin, an extracellular matrix protein. Decorin is involved in cardiac remodeling after physiologic stress and may be expressed differently by sex and age.

Lyme meningitis was more likely in children of both sexes, male adolescents, and young adult men in this study population. Lyme meningitis has not previously been attributed to

![Seasonal distribution (percentage by month of diagnosis) of Lyme disease cases in MarketScan databases, by clinical manifestation, among patients from high-incidence states during 2005–2014 (n = 88,022).](image-url)
any particular risk group. However, an increase in intracranial pressure accompanying meningitis caused by *B. burgdorferi* infection is recognized predominantly in children [26]. There are several potential explanations for a propensity of Lyme meningitis to affect children and young men. Meningitis of many etiologies typically affects children and young adults, for pathophysiologic (naive or weakened immune system) or environmental (eg, college setting) reasons. Characteristic EM only
CONCLUSIONS

Using medical claims data, we identified populations at increased risk for disseminated LD that differ from the LD population as a whole. These manifestations of LD cause serious illness and warrant characterizing to promote public health and clinical interventions, especially because these manifestations may overlap with other conditions.

Further study into the biological or behavioral differences in sex and age groups presenting with serious LD manifestations is important to improve understanding of disease pathophysiology. These findings may be used by healthcare providers and public health practitioners to improve prevention and early recognition of severe LD in at-risk populations, particularly for patients who live in or have visited a high-incidence LD region during summer months.

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TECHNICAL APPENDIX

Codes from the International Classification of Diseases, Ninth Revision, Clinical Modification for Established Manifestations of Lyme Disease or Plausible Coinfections

Arthritis codiagnosis (code)
- Pyrogenic arthritis (711.0x)
- Arthropathy associated with other bacterial disease (711.4)

Antimicrobial Drugs Used for Treatment of Lyme Disease and Establishment of Inclusion Criteria for Outpatient Events

Amoxicillin
- Amoxicillin/clavulanic acid

Azithromycin or azithromycin dihydrate

Ceftriaxone sodium

Penicillin G (benzathine, procaine, or potassium)

Tetracycline hydrochloride

These antimicrobial drugs are not formally recommended for treatment of Lyme disease but are closely related to the recommended drug or are a known historical treatment that some practitioners might still prescribe.