TITLE PAGE

Full title: **Clinical presentation of Lyme disease cases in the higher-risk region of Québec: a retrospective descriptive study**

Running Head: Lyme in La Pommeraie

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ABSTRACT

Background: Lyme disease is emerging in Canada and Québec. This study aimed to describe the use of Lyme serology in La Pommeraie health region between 2012-2015, and to describe the clinical presentations of people with positive serology.

Methods: All patients for whom a Lyme serology was requested at the Brome-Missisquoi-Perkins Hospital's laboratory between 2012-2015 were identified and their charts were reviewed for serology results. Laboratory diagnosis was based on a two-tiered testing. A retrospective chart review for clinical presentation was then conducted for people assessed at the hospital or at the Family Medicine Unit La Pommeraie.

Results: Between 2012-2015, 720 persons were investigated for Lyme disease, which represent a fivefold increase in serology requests from 2012 (53) to 2015 (273). A total of 59 cases were positive for IgM (50) or IgG only (9) by two-tiered testing. For 29 IgM positive cases, the most common symptoms were fever (59%), fatigue (48%), myalgia (41%) and erythema migrans (48%), but 79% had some cutaneous manifestation. Tick bite was reported by only 38%. Lyme serology was IgM or IgG positive for 34% of people presenting with erythema migrans and investigated for Lyme disease.

Interpretations: There has been a clear increase in Lyme awareness and serology requests in La Pommeraie area over recent years. Cutaneous manifestations, fever and myalgia remain common features of IgM positive cases. The majority did not report a history of tick bite.

Key Words: Lyme, tick, *Borrelia burgdorferi*, Family Medicine, Resident, Québec

INTRODUCTION

Lyme disease is emerging in Canada.[1-3] In Quebec, only 2 cases were reported in 2004, compared to 160 cases in 2015.[4, 5] This disease is caused by the spirochete *Borrelia burgdorferi* present in the saliva of infected ticks.[5] Untreated, the infection can affect multiple organs, including the skin, the heart, the eyes, the central and peripheral nervous system, and the musculoskeletal system.[5] Quebec guidelines recommends a Lyme serology in the presence of erythema migrans or in the presence of any symptom suggestive of Lyme disease, even without an observed tick bite.[6] Symptoms include fatigue, headache, anorexia, fever, regional lymphadenopathy, myalgia and diffuse arthralgia.[6] These are non-specific complaints frequently encountered in primary care, which makes it difficult for primary caregivers or emergency physicians to determine when to order Lyme disease serology.

Considering the serious consequences of this condition and its increasing prevalence, medical residents from the Family Medicine Unit La Pommeraie (Université de Sherbrooke) designed this research project to inform clinical decision-making on screening for Lyme disease. The first objective of this study was to review the use of serology requests sent to the Brome-Missisquoi-Perkins hospital microbiology laboratory between 2012 and 2015, and the proportion of positive results. The second objective was to describe the most commonly reported clinical presentations of the laboratory confirmed cases and to examine the proportion of confirmed diagnoses in people presenting with erythema migrans and investigated for Lyme disease.

METHODS

Study setting

An analysis of the Public Health expertise and reference centres of Quebec ranked municipalities by level of risk.[7] The only high-risk municipality in Quebec was Farnham, where more than 20% of ticks were infected with *Borrelia burgdorferi*.[7] This municipality as well as five others considered as moderate risk (Brigham, Bromont, Cowansville, Saint-Armand, and Sutton),[7] are served by the Brome-Missisquoi-Perkins Hospital, located in Cowansville. This hospital is a primary care hospital offering outpatients and inpatients health care services, with 84 short-term beds and 12 long-term beds. It is part of the Centre intégré universitaire de santé et de services sociaux de l'Estrie – Centre hospitalier universitaire de Sherbrooke, and provides medical services for the population living in the local health and social service network La Pommeraie, i.e. 22 municipalities: Abercorn, Frelighsburg, Saint-Armand, Pike River, Stanbridge Station, Bedford Township, Stanbridge East, Dunham, Sutton, West Bolton, Brome, Brome Lake, Cowansville, East Farnham, Brigham, Saint-Ignace-de-Stanbridge, Notre-Dame-de-Stanbridge, Sainte-Sabine, Farnham, Ange-Gardien, and Sainte-Brigide-d'Iberville. During the study period (2012-2015), it also provided services for Bromont and Waterloo. Lyme serology ordered by a physician working in this hospital or at one of the 14 medical clinics on this local network are first sent to the microbiology laboratory of the Brome-Missisquoi-Perkins hospital. In Québec, laboratory diagnosis is made through a two-tiered testing as recommended by the Center for Diseases Control and Prevention[8]; specimens are first tested through enzyme immunoassay (EIA), and only specimens that are EIA-positive are sent for further analysis to the National Microbiology Laboratory in Winnipeg where EIA is repeated and positive results are processed to complete Western Blot testing for IgM and IgG[6]. We began our data collection in 2012 because there was only 28 cases of Lyme disease reported in Québec in 2011, and the rising incidence began thereafter.[4]

Study design

The study was a retrospective descriptive study based on chart reviews, and ethics approval was provided by the research ethics board of the Centre de Recherche du Centre Hospitalier Universitaire de Sherbrooke.

For the first objective, we included all people who had Lyme serology requested at the microbiology laboratory of the Brome-Missisquoi-Perkins Hospital between January 1st 2012 and December 31st 2015, as provided by the microbiology laboratory of the hospital. Electronic chart reviews were conducted to collect gender, age at testing, postal code of residence, and Lyme serology results from both local and National Microbiology Laboratory. Serology kits used in most cases were VIDAS for the first local test, and Immunetics C6 and Euroimmun Western Blot at the National Laboratory.

For the second objective, we included the same study population as for objective 1, and excluded all people for whom the medical charts of the Brome-Missisquoi-Perkins Hospital or the Family Medicine Unit LaPommeraie did not contain information related to the Lyme serology requests, were unreadable or incomplete. The medical chart of people assessed in other outpatient medical clinics of the local health network La Pommeraie was not accessible by our research team. Medical charts were reviewed by the 5 first co-authors using a paper case report form created and piloted at the beginning of the study to standardize data collection between researchers. The form required simple box ticking (yes/no or multiple choice) or date entry. Minimal text entry was possible when "other" was selected. The information collected included data specific risk factors (history of travel or tick bite); systemic signs and symptoms reported (fever, fatigue, headache, anorexia, lymphadenopathy, malaises, lethargy or alteration in level of

consciousness); skin manifestations (erythema migrans or other cutaneous lesion); musculoskeletal symptoms (myalgia, arthralgia, migratory pains, arthritis, other); neurological signs or symptoms (nuchal rigidity, facial paralysis, meningitis, encephalitis, polyradiculopathy, other); cardiac manifestations (atrial-ventricular blocks, myocarditis, pericarditis, other) and ophthalmologic manifestation (conjunctivitis, keratitis, uveitis, optic neuritis, other). Case report forms were formatted to allow scanning using Teleform software for data entry. All data entered was then reviewed for verification of concordance with the paper forms.

Statistical analyses

Descriptive analyses with 95% confidence intervals (95%CI) were calculated to answer the study objectives. Only the results of the confirmatory IgM and IgG serologies performed at the National Microbiology laboratory were considered to identify cases. If a person had more than one serology completed, the first test with positive IgM was retained. If never positive for IgM, we retained the first specimen positive for IgG, or the first test if always negative. For the chart review, signs and symptoms were categorized as "no" if they were not mentioned in the medical note. Statistical analyses were performed with Stata software, version 11.2.

RESULTS

Total Lyme serology performed at BMP hospital

Of the 720 persons investigated for Lyme disease at the Brome-Missisquoi-Perkins Hospital laboratory between January 1st 2012 and December 31st 2015, 3 were excluded because their results were unavailable. **Figure 1** presents a flow diagram of their results. In these 717, 59 were either positive for IgM (50) or IgG only (9). **Figure 2a)** presents the number of tests

requested per year, and the proportion of those that were positive. Over the course of the 4 years studied, the annual number of requests for serology increased by almost fivefold, from 53 in 2012 to 273 in 2015. The proportion of positive local tests (first EIA) also increased, but the number of confirmed cases through Western Blot testing at the National Laboratory only increased from 2012 (3 cases) to 2013, and remained at around 18-19 cases per year from 2013 to 2015. **Figure 1b)** demonstrates the results per month of the year (all years combined). Considerably more serology requests and laboratory diagnoses were made between June and October, particularly in July. **Table 1** presents demographic characteristics of the people with confirmed positive IgM or IgG serology. The majority were men (67.80%, 95%CI: 54.36-79.38), aged 20-39 (35.59%, 95%CI: 23.55-49.13) or 40-59 (28.81%, 95%CI: 17.76-42.08), and lived in Cowansville (27.12%, 95%CI: 16.36-40.27) or Bromont (32.30%, 95%CI: 20.62-45.64).

Clinical presentation of people with a positive Lyme serology result

Medical chart review was completed for 38 of the 59 laboratory confirmed cases; 29 were IgM positive, and 9 were IgM negative but IgG positive. All of them were investigated in outpatient contexts; 22 (57.89%) were assessed in the emergency room, and 16 (42.11%) were seen at outpatient clinics.

Signs and symptoms reported for these confirmed cases of Lyme disease are presented in **Table 2**, for all verified symptoms. Fever (52.63%, 95%CI: 35.82-69.02), fatigue (47.37%, 95%CI: 30.98-64.18), headaches (31.58%, 95%CI: 17.50-48.65), myalgia (39.47%, 95%CI: 24.04-56.61) were commonly reported. Erythema migrans was specifically reported in 39.47% (95%CI: 24.04-56.61) of medical charts, and this proportion reached 48.28% (95%CI: 29.45-67.47) for people who were positive for IgM. Other cutaneous symptoms such as rash or

cellulitis were also commonly reported, such that cutaneous manifestations were present in 71.05% (95%CI: 54.10-84.58) of cases. For people positive for IgM, 79.31% (95%CI: 60.28-92.01) had reports of cutaneous manifestations. Four cases presented with facial paralysis (10.53%, 95%CI: 2.94-24.80), but otherwise neurological, cardiac and ophthalmic presentations were rare. A tick bite was reported by 31.58% (95%CI: 17.50-48.65) of cases and 37.93% (95%CI: 20.69-57.74) of IgM positive cases.

Of the 278 people investigated for Lyme disease and for whom medical chart could be reviewed, 44 (15.83%, 95%CI: 11.74-20.66) were reported to present with erythema migrans. Therefore, of the 44 people presenting with erythema migrans as per the medical chart, 14 (31.82%, 95%CI: 18.61-47.58) had IgM positive serology, 1 (2.27%, 95%CI: 0.06-12.02) were only positive for IgG and 29 (65.91%, 95%CI: 50.08-79.51) did not have a laboratory diagnosis of Lyme disease.

INTERPRETATION

Main findings

We identified a steep rise in Lyme serology requests at Brome-Missisquoi-Perkins Hospital between 2012 and 2015, but a relatively stable number of cases per year (18-19) from 2013 to 2015. Confirmed cases were most common in men, aged 20 to 59 years old, and living in Cowansville or Bromont. Only 38% reported a tick bite. The most common symptoms reported for cases of laboratory confirmed Lyme disease were fever, fatigue, myalgia and headaches. Cutaneous findings were present in 71% of cases, but erythema migrans was specifically identified in only 39% of all cases, and 48% of IgM positive cases.

Explanations and comparison with other studies

The progression in the number of Lyme disease cases in this area is consistent with the migration of ticks from the northeast United States to Canada[9]. Although a study from the National Public Health Institute of Québec identified that Farnham was the only high-risk region in the province, we only had 4 cases of Farnham seen at the hospital for Lyme disease investigation. It is possible that people living in Farnham consulted in other regions to complete their lab results, so we cannot draw specific conclusions about this area. However, the high number of cases identified in Bromont and Cowansville should raise concern that people living in those areas are at high risk, whether this being due to the presence of ticks in their residential areas, or to a higher exposure to ticks through a higher prevalence of practicing outdoor activities in wooded areas. Tick bites were only reported by 38%, which is consistent with previous reports.[6] This low frequency could also be due to the limitations of retrospective studies, as physician questionnaires and chart reporting on tick bites may vary, especially in cases where Lyme was not considered as the most likely diagnosis.

The most commonly reported symptoms are not specific to Lyme disease, and illustrate the challenge in properly diagnosing Lyme disease. Cutaneous manifestations were very common, although many were not reported as erythema migrans but as rash or cellulitis. Misclassification is possible here as some of the undefined rash or cellulitis could have been erythema migrans, and it is not possible from retrospective chart review to verify if the erythema migrans were properly diagnosed. A recent publication suggested that physicians in Québec possibly misdiagnosed erythema migrans in 63% of patients, requested unnecessary serology in 56%, and that 97% of prophylaxis prescription were not justified.[10] Clinical diagnosis of Lyme disease can be done without serology testing when a patient presents with a typical

erythema migrans of at least 5 cm, occurring in season and with a history of exposure to ticks in which case antibiotic treatment should be given irrespective serological results.[11-14] However, the 2013 Québec recommendations suggest serology testing in the presence of any signs or symptoms compatible with Lyme disease.[6] Our results confirms that fever, fatigue, myalgia and cutaneous presentations remain the most likely presentation of Lyme disease. Although only four cases in our study population presented with facial paralysis, a recent report from England suggests that the combination of Bell's palsy with Lyme disease is increasing, and recommended physicians to suspect Lyme disease when seeing patients with facial palsy.[15]

Limitations

The main limitation of this study is the potential information bias due to the retrospective nature of the study, and selection bias since the medical records were limited to those of the hospital. It is possible that cases presenting with classic clinical features of erythema migrans, fever and history of tick bites were most likely to be managed entirely out of the hospital and that more atypical presentations were most likely to be referred to the hospital for specialist opinion. Also, it was not possible to properly obtain the duration of symptoms from chart reviews, information that should be considered in the clinical diagnosis of Lyme disease. We thus relied on laboratory diagnosis. Since the majority of our cases were IgM positive, we could not identify striking differences between acute or later presentations. We could also not assess pet ownership as a previously reported risk factor [16, 17]. The generalizability of results may be limited for other areas in Canada, as the prevalence of Lyme disease varies considerably by region.

Conclusions and implications for practice and future research

The rising incidence of Lyme disease is an important public health concern in Canada, and data from areas with higher prevalence may guide primary care physicians in properly

including Lyme disease in their differential diagnosis, and use Lyme serology optimally. Unfortunately, serology remains an imperfect test to diagnose this disease, and more accurate diagnostic tests with better sensitivity and specificity would be helpful.

Figure 1: Flow diagram of the study cases identification

Footnote: Cases with positive IgM include 13 IgG negative, 12 IgG positive and 4 undetermined for IgG. EIA: Enzyme Immunoassay.

Figure 2: Absolute number of persons for whom a Lyme serology request was sent to the Brome-Missisquoi-Perkins Hospital by year (Figure 2a) and by month (Figure 2b) to demonstrate seasonal and temporal variations. Positive results are in dark grey, and negative results in pale grey.

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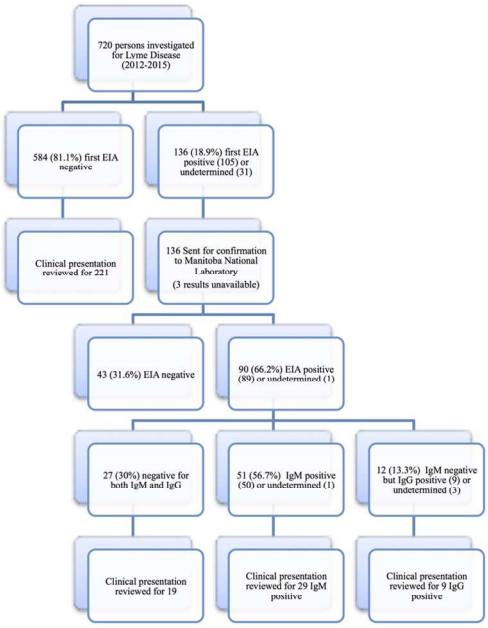

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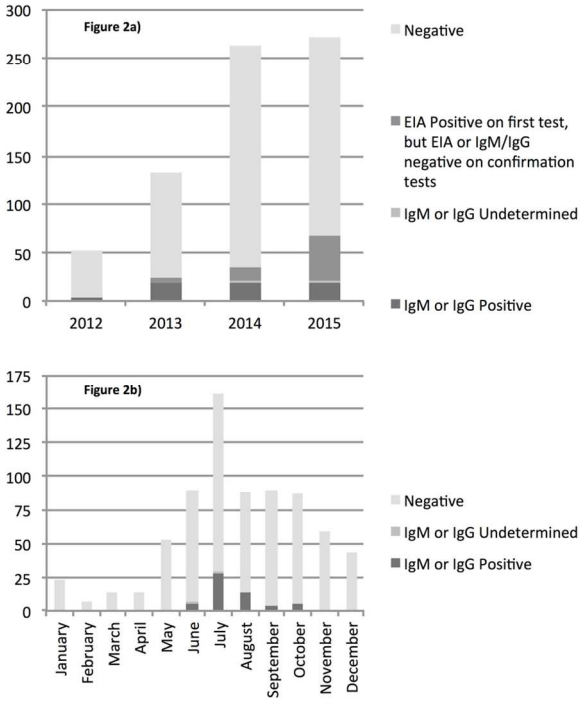

Figure 2: Absolute number of persons for whom a Lyme serology request was sent to the Brome-Missisquoi-Perkins Hospital by year (Figure 2a) and by month (Figure 2b) to demonstrate seasonal and temporal variations. Positive results are in dark grey, and negative results in pale grey.

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Table 1. Characteristics of the study population with a positive Lyme serology (IgM or IgG) for requested through the Brome-Missisquoi-Perkins Hospital

Characteristic	All (IgM or IgG positive) N=59	IgM positive N=50
	N (%)	N (%)
Age categories (years)		
<= 19	7 (11.86)	5 (10.00)
20-39	21 (35.59)	18 (36.00)
40-59	17 (28.81)	14 (28.00)
60+	14 (23.73)	13 (26.00)
Sex		
Male	40 (67.80)	34 68.00)
Female	19 (32.20)	16 (32.00)
Area of residence		
Lac Brome	11 (18.64)	9 (18.00)
Bedford	8 (13.56)	8 (16.00)
Cowansville	16 (27.12)	12 (24.00)
Bromont	19 (32.20)	18 (36.00)
Farnham	2 (3.39)	1 (2.00)
Other	3 (5.08)	2 (4.00)
Year of serology		
2012	3 (5.08)	2 (4.00)
2013	19 (32.20)	18 (36.00)
2014	19 (32.20)	17 (34.00)
2015	18 (30.51)	13 (26.00)

Table 2. Clinical history reported in the medical charts of Brome-Missisquoi-Perkins Hospital or La Pommeraie Family Medicine Unit for patients with positive Lyme serology

Signs and Symptoms	All (IgM or IgG positive) N=38	IgM positive N=29
	N (%)	N (%)
Systemic Symptoms		
Any	30 (78.95)	25 (86.21)
Fever (reported or objective)	20 (52.63)	17 (58.62)
Fatigue	18 (47.37)	14 (48.28)
Headaches	12 (31.58)	10 (34.48)
Anorexia	5 (13.16)	5 (17.24)
Lymphadenopathy	3 (7.89)	3 (10.34)
Malaise	9 (23.68)	7 (24.14)
Lethargy	2 (5.26)	1 (3.45)
Cutaneous Symptoms		
Any	27 (71.05)	23 (79.31)
Erythema Migrans	15 (39.47)	14 (48.28)
Rash (not specified as Erythema Migrans)	8 (21.05)	6 (20.69)
Cellulitis	2 (5.26)	2 (6.90)
Ulcers	0	0
Musculo-skeletal symptoms		
Any	20 (52.63)	13 (44.83)
Myalgia	15 (39.47)	12 (41.38)
Arthralgia	7 (18.42)	4 (13.79)
Migratory pains	3 (7.89)	3 (10.34)
Arthritis	4 (10.53)	1 (3.45)
Neurological Symptoms		
Any	7 (18.42)	5 (17.24)
Nuchal rigidity	2 (5.26)	1 (3.45)
Facial Paralysis	4 (10.53)	3 (10.34)
Meningitis	0	0
Encephalitis	0	0
Polyradiculopathy	1 (2.63)	1 (3.45)
Cardiac Symptoms		
Any	2 (5.26)	2 (6.90)
AV Block	2 (5.26)	2 (6.90)
Myocarditis	0	0
Pericarditis	0	0
Ophthalmic Symptoms		
Any	1 (2.63)	1 (3.45)
Conjunctivitis	1 (2.63)	1 (3.45)
Keratitis	0	0
Uveitis	0	0
Optic neuritis	0	0
Travel		
Reported travel in New England	3 (7.89)	3 (10.34)
Tick bite reported	12 (31.58)	11 (37.93)
Tick brought for analysis	0	0