Clinical Infectious Diseases

MAJOR ARTICLE

Prospective Evaluation of the Frequency and Severity of Symptoms in Lyme Disease Patients With Erythema Migrans Compared With Matched Controls at Baseline, 6 Months, and 12 Months

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(See the Editorial Commentary by Strle and Strle on pages 3125–7.)

Background. Erythema migrans is the most common clinical manifestation of Lyme disease. Despite antibiotic therapy, typically at least 10% of adult patients with erythema migrans experience persistence of at least 1 subjective symptom for ≥6 months (posttreatment Lyme disease symptoms [PTLDS]).

Methods. This study was designed to determine whether the frequency and severity (based on a visual analogue scale) of 12 particular symptoms in patients with erythema migrans (n = 52) differed from matched control subjects (n = 104) followed prospectively for 12 months.

Results. At baseline, patients with Lyme disease were more likely than controls to have at least 1 symptom ($P = .006$). Among symptomatic subjects, Lyme disease patients had a higher mean number of symptoms ($P < .001$) and a higher mean total symptom severity score ($P < .001$). At both 6 and 12 months, however, there were no significant differences for these variables and no significant differences in the frequency or severity of any of the 12 individual symptoms assessed. However, 10 patients were clinically assessed as having possible PTLDS.

Conclusions. Patients with erythema migrans were more likely than matched control subjects to be symptomatic at baseline with a greater symptom severity score, but this was not found at ≥6 months. Use of symptom survey data alone, however, was less likely to identify patients with possible PTLDS compared with individual clinical assessments. Because it is very challenging to be certain that the presence of long-term symptoms in a particular patient is correctly attributable to having had Lyme disease, an objective biomarker would be highly desirable.

Keywords. Lyme disease; PTLDS; *Borrelia burgdorferi*; posttreatment symptoms; outcome.

Erythema migrans is the most common clinical manifestation of Lyme disease. In addition to the skin lesion(s), approximately 65% (95% confidence interval, 52%–76%) of United States (US) patients with erythema migrans also have systemic symptoms, commonly including fatigue, headache, myalgias, and arthralgias [1]. Whether the frequency, severity, or type of these symptoms in adult patients with erythema migrans differs from matched control subjects followed prospectively in an identical way over the course of 12 months has not been systematically evaluated in the US. In this study, we report on 52 consecutively enrolled adult patients with erythema migrans and 104 matched control subjects followed over an approximately 1-year time period.

METHODS

Fifty-two adult patients with erythema migrans who had not received antibiotics at time of study entry and 104 control subjects matched for sex, ethnic group, and age within 5 years were enrolled into a 1-year prospective study, as described elsewhere [2–4]. All subjects were questioned using an 8-cm visual analogue scale (VAS) about whether any of 12 particular symptoms (fatigue, headache, stiff neck, joint pain, muscle pain, decreased appetite, difficulty with concentration/memory, feeling feverish/chilly, dizziness, tingling/abnormal sensation, nausea or vomiting, and cough) were present at the baseline visit and at the 6- and 12-month follow-up visits. At the 6- and 12-month follow-up visits, subjects without a particular symptom present

Received 2 October 2019; editorial decision 14 November 2019; accepted 2 January 2020; published online January 23, 2020.

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Clinical Infectious Diseases® 2020;71(12):3118–24

DOI: 10.1093/cid/ciz1215

on the day of the study visit were also asked about whether that symptom had been present since the last study visit and had lasted for at least 2 weeks. In this circumstance, the 8-cm VAS was completed by the study subject for the same 12 symptoms and designated as 6-month ≥2 week symptoms, or 12-month ≥2 week symptoms. For any reported symptom, the subject was interviewed to determine symptom duration and was both interviewed and examined to determine a possible etiology.

Control subjects were recruited from the primary care internal medicine practice located at the study site during the same Lyme disease season when the patients with erythema migrans were entered into the study. Control subjects were serially evaluated as described above for the Lyme disease patients and were assessed for the presence, severity and duration of the same 12 subjective symptoms.

Lyme disease patients with subjective symptoms that persisted for at least 6 months were clinically assessed by the study investigators to determine if they might have posttreatment Lyme disease symptoms (PTLDS). As there is no objective diagnostic test for PTLDS, all identified cases were considered to have "possible PTLDS."

Exclusion Criteria

Patients were excluded if they had had Lyme disease within the prior 12 months or if they had persistence of symptoms attributed to an episode of Lyme disease that had occurred >1 year earlier. Control subjects were excluded if they ever had Lyme disease in the past. Control subjects underwent 2-tier serologic testing for antibodies to *Borrelia burgdorferi* at the baseline visit and were excluded if found to be seropositive.

Both Lyme disease and control subjects were excluded if they were pregnant, were within 6 months postpartum, or were immunocompromised; if they had morbid obesity, untreated sleep apnea, narcolepsy, autoimmune disorders, or uncontrolled cardiopulmonary or endocrine disorders; or had been diagnosed with a malignancy within 2 years except for uncomplicated skin cancer. Additional exclusions included having a known current liver disease and having had any past or present diagnoses of a major depressive disorder with psychotic or melancholic features, other psychiatric disorders, dementia, anorexia nervosa or bulimia nervosa, or either drug abuse or alcoholism within the prior 2 years.

The study was approved by the institutional review board at New York Medical College (number 9949).

Other Assessments

Lyme disease patients and matched controls were also serially assessed for their health-related quality of life based on the Medical Outcomes Study 36-Item Short-Form General Health Survey version 2 (SF-36) [5]. The summary score on the physical component of the SF-36 (PCS) is discussed in this report, as in previous treatment trials of patients with PTLDS [6, 7]. The mean score for the general population has been normalized to be 50 ± 10. Scores <50 are considered below the norm for the general population.

Statistical Methods

Univariable comparisons between Lyme disease patients and control subjects were conducted using Fisher exact test for categorical data and independent *t* tests assuming unequal variances for continuous data. This approach was used for group comparisons for each time point specified. Symptom severity scores were compared among those patients in each study group who reported the symptom as present. Due to multiple comparisons, a *P* value of ≤ .01 was used as the cutoff for considering a difference to be statistically significant.

To verify the univariable comparisons, a linear mixed model was used to analyze change over time in severity scores for individual symptoms measured at baseline, 6 months, and 12 months. In this analysis, subjects who did not report a particular symptom were assigned a zero for the severity score of that symptom. A group-by-time interaction term was used to determine whether the change in severity scores was statistically significantly different between the Lyme disease patients and the control subjects over time. If the interaction term was statistically significant, a post hoc test between Lyme disease patients and controls was conducted at each time point, using Sidak procedure to adjust for multiple comparisons.

RESULTS

Fifty-two untreated adult patients with erythema migrans and no clinical evidence of an extracutaneous manifestation of Lyme disease and 104 closely matched control subjects with no history or serologic evidence of Lyme disease were entered into a 1-year prospective study (Table 1). The patients with erythema migrans were treated with antimicrobial regimens consistent with current guidelines beginning on the date of the baseline visit [8].

Compliance with follow-up at 6 months was 88.5% for Lyme disease patients vs 91.3% for control subjects (*P* = .57), and

Table 1. Demographics and Selected Other Characteristics of Study Subjects

Characteristic	Patients With Lyme Disease	Controls
No. enrolled	52	104
No. (%) evaluated at 6 mo	46 (88.5)	95 (91.3)
No. (%) evaluated at 12 mo	49 (94.2)	98 (94.2)
No. (%) evaluated at either 6 or 12 mo	50 (96.2)	101 (97.1)
Age, y, mean ± SD (median [range])	50.2 ± 15.7 (50.5 [20–86])	50.4 ± 15.0 (52.0 [20–85])
Male sex, %	65.4	65.4
White ethnicity, %	92.3	91.4
No. (%) with multiple EM skin lesions	21 (40.4)	NA

Abbreviations: EM, erythema migrans; NA, not applicable; SD, standard deviation.

compliance at 12 months was identical at 94.2% for both groups. Only 2 Lyme disease patients and only 3 control subjects failed to return for both the 6- and 12-month follow-up visits.

At the baseline visit, 75% of the Lyme disease patients had 1 or more of the 12 symptoms evaluated vs 51% of the matched controls ($P = .006$). At 6 months, 39.1% (18/46) of the evaluable Lyme disease patients had 1 or more of the 12 symptoms vs 51.6% (49/95) of the evaluable controls ($P = .21$), and at 12 months, 55.1% (27/49) of the evaluable Lyme disease patients had 1 or more of the 12 symptoms vs 51.0% (50/98) of the evaluable controls ($P = .73$). Even if we assumed that all 3 of the Lyme disease patients who did not return for the 12-month follow-up visit were symptomatic and that all 6 of the control subjects who did not return were asymptomatic, there would still have been no significant difference in the proportions of Lyme disease patients vs control study subjects who were symptomatic at that time point ($P = .31$).

At the baseline visit, the mean ± standard deviation number of symptoms reported by the symptomatic Lyme disease patients was significantly greater than the number reported by the symptomatic control subjects (4.15 ± 3.04 vs 2.02 ± 1.22, respectively; $P < .001$), but not at the later time points (Table 2). In addition, at baseline, 13 of the 52 (25.0%) Lyme disease patients had at least 6 symptoms compared with 1 of the 104 controls (1.0%) ($P < .0005$); at both 6 and 12 months, however, there was no significant difference (Table 3). At the baseline visit, the mean total symptom severity score based on the VAS of the symptomatic Lyme disease patients significantly exceeded that of the symptomatic control subjects ($P < .001$), but there was no statistically significant difference at the later time points (Table 2).

The frequency of the 12 individual symptoms at the baseline visit in descending order for the Lyme disease patients was fatigue (51.9%) (defined as tired/lack of energy), headache (36.5%), stiff neck (36.5%), joint pain (30.8%), muscle pain (28.9%), decreased appetite (26.9%), difficulty with concentration/memory (21.2%), feeling feverish/chilly (19.2%), feeling dizzy (19.2%), experiencing tingling/abnormal sensation (17.3%), nausea or vomiting (11.5%), and cough (11.5%). The frequency of all of these individual symptoms significantly exceeded that of the controls at the baseline visit except for joint pain, muscle pain, tingling/abnormal sensation, and cough (Table 4). At the baseline visit, the symptom severity score of fatigue, headache, and joint pain significantly exceeded that of the control subjects ($P < .01$). In contrast, at both the 12-month study visit and at the final visit (ie, at 12 or 6 months depending on compliance with follow-up), there were no significant differences in either the frequency of having a particular symptom or in the severity of the symptom for the Lyme disease patients vs the control subjects (Table 4). Results of a multivariable analysis using linear mixed models confirmed the univariable analyses, indicating that differences between the study groups in severity scores of individual symptoms at baseline largely disappeared by 6 and 12 months (data not shown).

Table 2. Number of Symptoms and Severity Level of Symptoms for Symptomatic Subjects

Time Point	Patients		Controls		*P* Value for Patients vs Controls	
	No. of Symptoms for Those With Symptoms	Total Severity Score	No. of Symptoms for Those With Symptoms	Total Severity Score	No. of Symptoms for Those With Symptoms	Total Severity Score
Baseline	4.15 ± 3.04 (1–11) (n = 39)	14.59 ± 15.44 (0.4–62.6)	2.02 ± 1.22 (1–6) (n = 53)	4.37 ± 5.10 (0.2–23.7)	<.001	<.001
6 mo	2.11 ± 1.29 (1–6) (n = 18)	7.38 ± 6.94 (1.7–29.1)	2.10 ± 1.31 (1–6) (n = 49)	4.41 ± 4.52 (0.2–22.1)	.98	.11
12 mo	1.78 ± 1.26 (1–6) (n = 27)	4.74 ± 4.32 (0.5–15.5)	1.84 ± 1.62 (1–8) (n = 50)	4.82 ± 5.78 (0.3–30.5)	.85	.91
Last visit[a]	1.78 ± 1.26 (1–6) (n = 27)	4.74 ± 4.32 (0.5–15.5)	1.88 ± 1.65 (1–8) (n = 52)	4.89 ± 5.70 (0.3–30.5)	.75	.86
6 mo, ≥2 wk	1.91 ± 1.24 (1–5) (n = 11)	7.61 ± 5.97 (2.2–20.8)	1.23 ± 0.52 (1–3) (n = 22)	3.88 ± 3.14 (0.6–14.4)	.12	.09
12 mo, ≥2 wk	1.86 ± 1.30 (1–5) (n = 14)	7.98 ± 6.21 (1.2–25.3) (n = 13)[b]	1.96 ± 1.46 (1–6) (n = 25)	7.32 ± 7.31 (0.7–30.4)	.83	.95

Data are presented as mean ± standard deviation (range) unless otherwise indicated.

[a]Last visit was at 12 months or 6 months depending on compliance.

[b]For 1 subject of the 14 with symptoms, the severity score was not available.

Table 3. Frequency of 6 or More Symptoms at Each Time Point

Time Point	Patients	Controls	*P* Value
Baseline	13/52 (25.0)	1/104 (1.0)	<.0005
6 mo	1/46 (2.2)	1/95 (1.1)	.55
12 mo	1/49 (2.0)	4/98 (4.1)	.67
Last visit[a]	1/50 (2.0)	4/101 (4.0)	1.00
6 mo, ≥2 wk	0/46 (0)	0/95 (0)	1.00
12 mo, ≥2 wk	0/49 (0)	1/98 (1.0)	1.00

Data are presented as no./No. (%) unless otherwise indicated.
[a]Last visit was at 12 months or 6 months depending on compliance.

The frequency of having difficulty with concentration or memory in the Lyme disease patients, a symptom thought to be associated with PTLDS [6–10], was more than twice that found for the controls at the 12-month visit (Table 4); however, 6 additional controls had mentioned that this symptom had been present and lasted for at least 2 weeks when questioned using the 12-month ≥2 week symptom survey. In contrast, only 1 additional Lyme disease patient had mentioned that this symptom had been present for at least 2 weeks based on the 12-month ≥2 week evaluation, but was not present on the date of the 12-month visit. Thus, at the 12-month study visit, 7 (6 + 1) Lyme disease patients had mentioned this symptom (7/49 [14.3%]) vs 11 (5 + 6) of the controls (11/98 [11.2%]) ($P = .60$). In terms of meeting criteria for PTLDS, for the purpose of this study, the symptoms had to have persisted, at least intermittently, for ≥6 months [8]. Therefore, if we restricted the analysis to just those cases in which the symptom of difficulty with concentration or memory had lasted for at least 6 months, irrespective of whether it was noted on the date of the 12 month visit, per se, or instead noted at the 12-month ≥2 week symptom survey, then the comparison is 5 of 49 (10.2%) vs 5 of 98 (5.1%) ($P = .31$; Table 5).

Additionally, at the 12-month study visit, more Lyme disease patients than controls had fatigue (another symptom that has been associated with PTLDS [4, 6–8]) that had been present for at least 6 months (4/49 [8.2%] vs 5/98 [5.1%], respectively; $P = .48$; Table 5). Based on the 12-month ≥2 week assessment, however, an additional 2 control subjects vs 0 Lyme disease patients had fatigue of at least 6 months' duration, bringing the total number to 7 of 98 (7.1%). Finally, although there was a nearly 6-fold higher frequency of a decrease in appetite in Lyme disease patients compared with control subjects at the 12-month evaluation, for only 1 Lyme disease patient was this symptom present for at least 6 months, suggesting an etiology other than PTLDS (Table 5).

Of note, 3 particular symptoms that have been associated with PTLDS, such as stiff neck, joint pain, and muscle pain, that had been present for at least 6 months, were actually more commonly found in the control group than in the Lyme disease patients at the 12-month time point (Table 5). Including the numbers of such cases at the 12-month visit, plus the 12-month ≥2 week time point, resulted in a prevalence of joint pain of 22 of 98 (22.4%) for the control group vs 9 of 49 (18.4%) for the Lyme disease patients, and a prevalence of muscle pain of 10 of 98 (10.2%) for the control group vs 4 of 49 (8.2%) for the Lyme disease group. The prevalence of stiff neck, however, was unchanged: 9 of 98 (9.2%) for the control group vs 1 of 49 (2.0%) for the Lyme disease patients.

In addition, we evaluated the frequency with which the Lyme disease patients and the control subjects fell below the norm for the general population on the PCS of the SF-36 survey (Table 6). At baseline and 6 months, the proportion that fell below the population norm for the Lyme disease patients exceeded that of the control subjects, but the reverse was found at the 12-month time point; none of the differences was statistically significant.

Finally, we assessed the frequency of possible PTLDS based on the investigators' (G. P. W.; D. M.) clinical assessment at New York Medical College. As many as 10 Lyme disease patients were regarded as having possible PTLDS. A similar analysis done at Yale (investigator E. D. S.) using deidentified study records concluded that as many as 11 of the Lyme disease patients may have had PTLDS (the same 10 as found at New York Medical College plus 1 additional patient). Based on the New York Medical College assessment, 7 of the 10 Lyme disease patients with possible PTLDS were still symptomatic at the 12-month assessment, and all 7 had 1 or more of the 12 symptoms that were assessed in this study.

DISCUSSION

In multiple studies conducted both in the US and Europe, patients with early Lyme disease often have concomitant subjective symptoms in addition to the erythema migrans skin lesion [1, 8–14]. In Europe, several prospective studies have found that the frequency of such symptoms at 1-year follow-up is not significantly greater than that found for control subjects without Lyme disease [11–14]. In this prospective study conducted in the US, very similar findings were observed. In addition, the frequency that the PCS of the SF-36 survey was below the population norm was actually greater among the control subjects compared with the Lyme disease patents at the 1-year time point, although the difference was not statistically significant (Table 6). However, this is not the only way to look at these data. When the investigators evaluated the timing of the symptoms and their persistence in the absence of alternative explanations, up to 10 patients (ie, 20% of those with at least 6 months of follow-up) were regarded as having possible PTLDS, and for all 10 of these patients a similar conclusion was arrived at by an independent investigator based on a review of study records.

It may be possible to determine the existence of PTLDS based only on the Lyme disease patients' reports on the presence, severity, or duration of symptoms. However, given the high prevalence of these same symptoms in the general population, the sample sizes required to detect a significant difference from

Table 4. Baseline, 12-Month, and Last Visit[a] Symptoms with Severity Score for Symptomatic Subjects

	Patients		Controls		*P* Value	
Time Point	No. (%)	Severity Score	No. (%)	Severity Score	No. With Symptom	Severity Score
Tired/lack of energy						
Baseline	27/52 (51.9)	3.56 ± 1.98 (0.4–8.0)	23/104 (22.1)	1.82 ± 1.35 (0.1–5.6)	.0003	.001
12 mo	9/49 (18.4)	2.77 ± 1.81 (0.5–5.6)	17/98 (17.4)	3.29 ± 1.83 (0.5–6.5)	.66	.57
Last visit	9/50 (18.0)	2.77 ± 1.81 (0.5–5.6)	19/101 (18.8)	3.26 ± 1.77 (0.5–6.5)	1.00	.60
Headache						
Baseline	19/52 (36.5)	3.12 ± 2.16 (0.3–8.0)	7/104 (6.7)	1.13 ± 0.78 (0.1–2.7)	<.0001	.003
12 mo	3/49 (6.1)	3.63 ± 1.24 (2.0–5.0)	7/98 (7.1)	2.29 ± 2.02 (0.3–5.7)	1.00	.31
Last visit	3/50 (6.0)	3.63 ± 1.24 (2.0–5.0)	7/101 (6.9)	2.29 ± 2.02 (0.3–5.7)	1.00	.31
Stiff neck						
Baseline	19/52 (36.5)	3.85 ± 2.13 (0.1–7.5)	12/104 (11.5)	2.37 ± 1.55 (0.2–4.6)	.0005	.04
12 mo	2/49 (4.1)	1.7 ± 0.3 (1.4–2.0)	9/98 (9.2)	3.12 ± 1.93 (0.5–6.0)	.34	.09
Last visit	2/50 (4.0)	1.7 ± 0.3 (1.4–2.0)	9/101 (8.9)	3.12 ± 1.93 (0.5–6.0)	.34	.09
Joint pain						
Baseline	16/52 (30.8)	4.13 ± 1.92 (1.3–7.8)	26/104 (25.0)	2.46 ± 1.57 (0.7–7.5)	.45	.008
12 mo	11/49 (22.5)	2.64 ± 1.66 (0.4–5.8)	25/98 (25.5)	2.58 ± 1.64 (0.4–6.4)	.84	.93
Last visit	11/50 (22.0)	2.64 ± 1.66 (0.4–5.8)	26/101 (25.7)	2.64 ± 1.63 (0.4–6.4)	.69	.99
Muscle pain						
Baseline	15/52 (28.9)	3.71 ± 2.13 (0.1–7.4)	14/104 (13.5)	2.89 ± 1.98 (0.2–7.3)	.03	.31
12 mo	3/49 (6.1)	2.13 ± 0.69 (1.3–3.0)	11/98 (11.2)	2.46 ± 1.78 (0.7–6.0)	.77	.99
Last visit	3/50 (6.0)	2.13 ± 0.69 (1.3–3.0)	12/101 (11.9)	2.41 ± 1.71 (0.7–6.0)	.58	.93
Decrease in appetite						
Baseline	14/52 (26.9)	3.51 ± 2.3 (0.6–8.0)	1/104 (1.0)	1.8 ± 0.00 (1.8–1.8)	<.0001	1.00
12 mo	3/49 (6.1)	3.27 ± 2.47 (0.5–6.5)	1/98 (1.0)	4.0 ± 0.00 (4.0–4.0)	.11	1.00
Last visit	3/50 (6.0)	3.27 ± 2.47 (0.5–6.5)	2/101 (2.0)	2.45 ± 1.55 (0.9–4.0)	.33	.75
Difficulty concentrating/memory problems						
Baseline	11/52 (21.2)	3.56 ± 2.36 (0.3–7.6)	5/104 (4.8)	1.66 ± 1.45 (0.2–4.2)	.004	.09
12 mo	6/49 (12.2)	2.42 ± 1.95 (0.1–5.1)	5/98 (5.1)	3.04 ± 1.73 (0.5–5.9)	.18	.63
Last visit	6/50 (12.0)	2.42 ± 1.95 (0.1–5.1)	5/101 (5.0)	3.04 ± 1.73 (0.5–5.9)	.18	.63
Feverish/chilly						
Baseline	10/52 (19.2)	4.56 ± 2.16 (1.4–7.8)	0/104 (0)	0	<.0001	1.00
12 mo	0/49 (0)	0	0/98 (0)	0	1.00	1.00
Last visit	0/50 (0)	0	0/101 (0)	0	1.00	1.00
Dizzy						
Baseline	10/52 (19.2)	3.18 ± 2.04 (0.4–7.3)	1/104 (1.0)	3.4 ± 0 (3.4–3.4)	<.0001	1.00
12 mo	2/49 (4.1)	2.0 ± 0.8 (1.2–2.8)	4/98 (4.1)	1.33 ± 0.74 (0.7–2.5)	1.00	.55
Last visit	2/50 (4.0)	2.0 ± 0.8 (1.2–2.8)	4/101 (4.0)	1.33 ± 0.74 (0.7–2.5)	1.00	.55
Tingling/abnormal sensation						
Baseline	9/52 (17.3)	2.28 ± 1.43 (0.7–5.7)	7/104 (6.7)	1.63 ± 1.75 (0.1–5.1)	.05	.47
12 mo	4/49 (8.2)	3.28 ± 1.44 (1.0–5.0)	5/98 (5.1)	1.6 ± 0.94 (0.4–2.8)	1.00	.33
Last visit	4/50 (8.0)	3.28 ± 1.44 (1.0–5.0)	6/101 (5.9)	1.42 ± 0.95 (0.4–2.8)	1.00	.27
Nausea/vomiting						
Baseline	6/52 (11.5)	2.85 ± 1.52 (1.5–5.8)	1/104 (1.0)	4.0 ± 0 (4.0–4.0)	.006	1.00
12 mo	1/49 (2.0)	3.8 ± 0 (3.8–3.8)	1/98 (1.0)	4.4 ± 0 (4.4–4.4)	1.00	1.00
Last visit	1/50 (2.0)	3.8 ± 0 (3.8–3.8)	1/101 (1.0)	4.4 ± 0 (4.4–4.4)	1.00	1.00
Cough						
Baseline	6/52 (11.5)	2.57 ± 1.25 (0.9–4.8)	10/104 (9.6)	2.01 ± 1.38 (0.5–4.1)	.78	.46
12 mo	4/49 (8.2)	2.05 ± 1.19 (0.9–3.8)	7/98 (7.1)	1.79 ± 0.85 (0.6–3.0)	1.00	.75
Last visit	4/50 (8.0)	2.05 ± 1.19 (0.9–3.8)	7/101 (6.9)	1.79 ± 0.85 (0.6–3.0)	1.00	.75

Data are presented as mean ± standard deviation (range) unless otherwise indicated.
[a]Last visit was at 12 months or 6 months depending on compliance.

non-Lyme disease controls would be much larger than in the present report. In our study, the difference between Lyme disease patients and control subjects in symptom prevalence at the follow-up time points was typically less than 10%. To illustrate, to detect an absolute value increase of 10% in the frequency of persistence of a particular symptom in Lyme disease patients

Table 5. Frequency of Symptoms That Had Been Present for ≥6 Months at the Time of the 12-Month Study Visit

Symptoms	Frequency in Patients With Lyme Disease (n = 49), No. (%)	Frequency in Controls (n = 98), No. (%)	*P* Value
Fatigue	4 (8.2)	5 (5.1)[a]	.48
Headache	0 (0)	0 (0)	1.00
Stiff neck	1 (2.0)	9 (9.2)	.17
Joint pain	8 (16.3)	21 (21.4)	.52
Muscle pain	3 (6.1)	8 (8.2)	.75
Decrease in appetite	1 (2.0)	0 (0)	.33
Difficulty with concentration/ memory	5 (10.2)	2 (2.0)[b]	.04
Feverish/chilly	0 (0)	0 (0)	1.00
Dizzy	0 (0)	0 (0)	1.00
Tingling/abnormal sensation	2 (4.1)	4 (4.1)	1.00
Nausea/vomiting	0 (0)	0 (0)	1.00
Cough	1 (2.0)	2 (2.0)	1.00

[a]The number increases to 7 (7.1%) if the control subjects' 12-month ≥2 week symptoms that had lasted for at least 6 months are also included, whereas the number did not change for the Lyme disease patients.
[b]The number increases to 5 (5.1%) if the control subjects' 12-month ≥2 week symptoms that had lasted for at least 6 months are also included, whereas the number did not change for the Lyme disease patients.

that occurs at a rate of approximately 30% in the general population (ie, 40% vs 30%), the sample size required to provide 80% power would be >350 subjects per group. For a symptom that occurs at a rate of 5% in the general adult population, to detect a 2-fold increase in the prevalence of this symptom (eg, 5% in the general population and 10% in Lyme disease patients), the sample size required for 80% power would be about 435 subjects per group. Also, it is important to emphasize that in our study we asked about the presence of any of 12 symptoms occurring on the day of the study visit. This methodologic approach may have served to underestimate the frequency of nonspecific symptoms in the study subjects. In certain other studies, the frequency of 8 particular symptoms was instead assessed over the preceding week. Using this approach, 83.4% of 205 non–Lyme disease control subjects had at least 1 symptom at the 12-month follow-up visit, including 76.1% who had fatigue, 53.7% who had arthralgias, 47.3% who had myalgias, 42.0% who had concentration difficulties, and 41.0% who had memory difficulties [13]. In addition, the control group used in our study did not have an acute infection at the time of enrollment. Had we instead used a control group who had, for example, cellulitis, the symptom frequency and severity at the baseline visit would likely have been more similar to that of the Lyme disease patients than was observed in the present study.

Table 6. Frequency With Which the Physical Component Summary From the Short-Form 36-Item Survey of Lyme Disease Patients and Controls Fell Below the General Population Norm at Baseline, 6 Months, and 12 Months

Time Point	Patients With Lyme Disease, No. (%)	Controls, No. (%)	*P* Value
Baseline	11/52 (21.2)	9/104 (8.7)	.04
6 mo	6/46 (13.0)	10/95 (10.5)	.78
12 mo	3/49 (6.1)	11/98 (11.2)	.39

In conclusion, possible PTLDS seems to occur in appropriately treated patients with early Lyme disease in the US at a frequency of ≥10% [11]. The use of symptom survey data alone is not nearly as likely to identify patients with possible PTLDS as are individual clinical assessments conducted by the study investigators who directly interacted with the patients. This was observed in this study and in other studies as well [13]. The fact that similar types of persistent subjective symptoms also occur in control subjects, however, suggests that there are multiple potential etiologies for these symptoms, making it very challenging to be certain that the presence of symptoms consistent with PTLDS in a particular patient is correctly attributable to having had Lyme disease. An objective biomarker of PTLDS would be highly desirable to avoid misclassification of patients.

Notes

Acknowledgments. The authors thank Shana Warner, Julia Singer, Elizabeth Flatley, and Lisa Giarratano for their assistance. This article is dedicated to the memory of their friend and colleague Dr Robert Nadelman.

Disclaimer. The findings and conclusions of this work are those of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention (CDC) or the National Institutes of Health (NIH).

Financial support. This work was supported by the CDC (grant number RO1 CK 000152 to G. P. W.); the Clinical and Translational Science Award (grant number UL1 TR000142 to E. D. S.) from the National Center for Advancing Translational Science at the NIH; and the NIH Roadmap for Medical Research (to E. D. S.).

Potential conflicts of interest. G. P. W. has received research grants from Immunetics, the Institute for Systems Biology, Rarecyte, and Quidel Corporation; owns equity in Abbott/AbbVie; has been an expert witness in malpractice cases involving Lyme disease; and is an unpaid board member of the American Lyme Disease Foundation. E. D. S. has received royalty payments from UpToDate; has received an honorarium from Sanofi to attend a meeting regarding a Lyme disease vaccine; has been an expert witness in malpractice cases involving Lyme disease; and is an unpaid board member of the American Lyme Disease Foundation. All other authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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