MAJOR ARTICLE

Long-term Assessment of Post-Treatment Symptoms in Patients With Culture-Confirmed Early Lyme Disease

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Background. Lyme disease patients with erythema migrans are said to have post-treatment Lyme disease symptoms (PTLDS) if there is persistence of subjective symptoms for at least 6 months following antibiotic treatment and resolution of the skin lesion. The purpose of this study was to characterize PTLDS in patients with culture-confirmed early Lyme disease followed for >10 years.

Methods. Adult patients with erythema migrans with a positive skin or blood culture for *Borrelia burgdorferi* were enrolled in a prospective study beginning in 1991 and followed up at 6 months and annually thereafter to determine the long-term outcome of this infection. The genotype of the infecting strain of *B. burgdorferi* was evaluated in subjects with PTLDS.

Results. One hundred twenty-eight subjects with culture-confirmed early Lyme disease, of whom 55% were male, were followed for a mean ± SD of 14.98 ± 2.71 years (median = 15 years; range = 11–20 years). Fourteen (10.9%) were regarded as having possible PTLDS, but only 6 (4.7%) had PTLDS documented at their last study visit. Nine (64.3%) had only a single symptom. None of the 6 with PTLDS at their last visit was considered to be functionally impaired by the symptom(s). PTLDS was not associated with a particular genotype of *B. burgdorferi*.

Conclusions. PTLDS may persist for >10 years in some patients with culture-confirmed early Lyme disease. Such long-standing symptoms were not associated with functional impairment or a particular strain of *B. burgdorferi*.

Keywords. Lyme disease; Lyme; post-treatment Lyme disease symptoms; *Borrelia burgdorferi*; erythema migrans.

Early Lyme disease is associated with a characteristic skin lesion, referred to as erythema migrans (EM); this lesion occurs at the site where the vector *Ixodes* tick inoculated *Borrelia burgdorferi*, the etiologic agent, into the skin. This manifestation of Lyme disease, as well as the extracutaneous manifestations of this infection involving the nervous system, heart, or joints, may be accompanied by a variety of subjective symptoms, including fatigue, arthralgias, myalgias, headache, neck pain, paresthesias, and memory or concentration difficulties [1]. A variety of antibiotics are recognized to be highly effective in resolving the EM and associated symptoms, but a minority of patients may continue to have 1 or more of the subjective complaints that had occurred coincident with, or shortly after, the EM [1]. These symptoms may be referred to as post-treatment Lyme disease symptoms (PTLDS). In 8 studies of patients with EM, the frequency of PTLDS at ≥6 months after treatment varied from 0% to 40.8%, with a median value of 11.5% [2]. In an unknown proportion of patients, such symptoms are so severe that they interfere with functionality, which has been referred to by some authorities as post-treatment Lyme disease syndrome [1].

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In this study, we report on the frequency, characteristics, and severity of PTLDS in patients with culture-confirmed EM who were followed prospectively for 11–20 years.

METHODS

Adult patients with EM who consented to a skin biopsy and for whom the diagnosis was confirmed by recovery of *B. burgdorferi* from culture of a skin or blood sample were enrolled in a prospective study beginning in 1991, as described elsewhere [3–6]. Enrollment ended in the year 2000. Subjects were asked to return at 6 months and annually thereafter to determine the long-term outcome of this infection. Patients with concomitant possible neurologic or cardiac manifestations of Lyme disease were not excluded. At the baseline visit, the patients were treated with antibiotics that are usually effective for *B. burgdorferi* infection [1]. At each study visit, the subjects were asked whether they were experiencing any of 12 particular symptoms on that day, as described elsewhere [7]. They were also asked to estimate the severity of each of these symptoms based on an 8-cm long visual analogue scale. A score of 0 meant that the symptom was not present, and a score of 8 indicated that the symptom was "extreme/could not be worse." Patients were also encouraged to report on any other symptoms or conditions that they had experienced since the last visit. Symptom duration was tabulated for those symptoms present at the prior visit but not present at the current visit. Medications, including use of intercurrent antibiotics, were recorded. An electrocardiogram was performed at the baseline visit.

During the years 2011–2013, the participants who returned to the study center underwent additional evaluations, including (1) an assessment of their health-related quality of life based on the self-administered medical outcomes study 36-item short-form General Health Survey version 2 (SF-36v2) [6]; (2) an assessment of whether there was evidence to support a diagnosis of fibromyalgia at that visit based on interview criteria and/or on a tender point examination [5]; and (3) an assessment of fatigue based on the Fatigue Severity Scale 11 (FSS-11), which evaluates fatigue over the prior 2 weeks [4]. The results of these investigations have been previously published [4–6].

The study was conducted in New York State and was approved by the institutional review board of New York Medical College.

Case Definitions

Subjects were regarded as having PTLDS if the symptoms were otherwise unexplained and if the symptoms developed at the time of presentation (or were intensified over the subject's pre–Lyme disease symptoms) or within 6 months of the time of diagnosis of early Lyme disease and lasted for at least 6 months following the completion of antibiotic therapy. Because of the nonspecificity of these kinds of symptoms and because of the absence of any marker or diagnostic test for PTLDS, for the purpose of this analysis no case was considered as definite PTLDS, only as possible. Aside from obtaining a medical history and performing a physical examination, no diagnostic evaluations for subjects with these symptoms were done on a routine basis. It was recognized that PTLDS may be intermittent [3, 4]. Thus, symptoms were still categorized as PTLDS at an annual follow-up visit even if not present on the day of each of the prior visits, provided they that they were indistinguishable from what the subject had been experiencing, were occurring with an intermittent pattern, and there was no other apparent explanation. Subjects were considered to have post–Lyme disease syndrome if the symptoms were so severe that they interfered with functionality based on direct questioning at the time of the final visit [1].

Laboratory Methods: Serology

Testing for antibody to *B. burgdorferi* was done by an enzyme immunoassay using a whole-cell sonicate of *B. burgdorferi* as the antigen or by the C6 Lyme ELISA kit (Immunetics, Boston, Massachusetts) [3, 4].

Laboratory Methods: Strain Typing

The genotype of the strains of *B. burgdorferi* that were recovered by culture of skin biopsy or blood samples from the study subjects was determined on the basis of restriction fragment-length polymorphism of the 16S–23S rRNA intergenic spacer and classified as ribosomal spacer type 1, 2, or 3. The genotype of most isolates was also determined based on the DNA sequence of the outer surface protein C gene. The methodology for both of these typing methods has been previously published [8].

Statistical Methods

For continuous variables, independent sample *t* tests, assuming equal variances, were used. For categorical variables, Fisher's exact test was used. A *P* value of .01 was considered as significant in view of the multiple comparisons that were performed.

RESULTS

One hundred twenty-eight subjects with culture-confirmed early Lyme disease, whose mean ± standard deviation (SD) age at study entry was 48.58 years ± 11.57 years, were followed for a mean ± SD of 14.98 ± 2.71 years (median = 15 years; range = 11–20 years). Seventy-one (55.5%) were male. Twenty-five (19.5%) had multiple EMs at presentation. One hundred four (81.3%) had additional symptoms besides the skin lesion at the baseline visit. The mean ± SD number of symptoms at the baseline visit was 3.41 ± 2.82 symptoms (median = 3 symptoms; range = 0–10 symptoms). The mean ± SD number of days of

Table 1. Comparison of 14 Subjects With Post-Treatment Lyme Disease Symptoms vs 114 Without

Variable	Patients Without Evidence of Post-Treatment Lyme Disease Symptoms	Patients With Possible Post-Treatment Lyme Disease Symptoms	*P* Value
No.	114	14	
No. males	64 (56.1)	7 (50.0)	.78
Age at baseline visit in years ± SD (range)	48.27 ± 11.71 (25–76)	51 ± 10.44 (37–72)	.41
Mean no. of days of illness until baseline visit ± SD (range)	5.82 ± 7.33 (0–42)	4.29 ± 5.01 (0–16)	.45
Single EM at baseline	95 (83.3)	8 (57.1)	.03
Symptomatic at study entry	91 (79.8)	13 (92.9)	.47
Mean no. of symptoms ± SD at baseline visit (range)	3.28 ± 2.84 (0–10)	4.64 ± 2.56 (0–9)	.09
History of Lyme	22 (19.3)	1 (7.1)	.46
Intercurrent EM	27 (23.7)	2 (14.3)	.74
Antibiotics active against Lyme[a]	93 (81.6)	12 (85.7)	1.00
Lyme serologies consistently negative[b]	20 (17.5)	1 (7.1)	.46
≥50% of the Lyme serologies performed were reactive[b,c]	49 (43.0)	8 (57.1)	.40
No. with reactive Lyme serology at the baseline visit[c]	43 (44.3) (out of n = 97)	7 (53.9) (out of n = 13)	.56
Number with reactive Lyme serology at final visit[c]	49 (43.0)	4 (30.8) (out of n = 13)	.56
Mean no. of visits ± SD (range)	13.77 ± 3.76 (5–22)	13.57 ± 3.48 (8–19)	.85
Mean duration of visits ± SD (range), y	14.94 ± 2.70 (11–20)	15.29 ± 2.89 (11–20)	.65
FSS-11 score at last visit (range)	2.02 ± 1.27 (1–7) (out of n = 88)	2.22 ± 1.61 (1–6.7) (out of n = 12)	.62
Intercurrent comorbidity	81 (71.1)	8 (57.1)	.36
Intercurrent hospitalizations	54 (47.4)	8 (57.1)	.58

Data are no. (%) unless otherwise noted.

Abbreviations: EM, erythema migrans; FSS-11, Fatigue Severity Scale 11; SD, standard deviation.

[a] Antibiotics prescribed for reasons other than Lyme disease.

[b] Serologic testing was performed with blood samples obtained at each follow-up visit.

[c] Reactive serology indicates that a first-tier serologic test was positive or equivocal.

illness until the baseline visit was 5.44 ± 6.69 days (median = 3 days; range = 0–42 days). If the patient presented on the same day as the symptoms started, this was tabulated as 0 days of illness.

Fourteen (10.9%) of the 128 subjects were regarded as having possible PTLDS, although only 6 (4.7%) had PTLDS documented at their last study visit. A comparison of those 14 subjects with

Table 2. Comparison of Baseline Symptoms in 14 Subjects With Post-Treatment Lyme Disease Symptoms vs 114 Without

Symptom at First Visit	Patients Without Evidence of PTLDS	Patients With Possible PTLDS	*P* Value
Number	114	14	
Loss of appetite	25 (21.9)	5 (35.7)	.31
Joint pain	50 (43.9)	7 (50.0)	.78
Cough	15 (13.2)	2 (14.3)	1.00
Dizziness	19 (16.7)	5 (35.7)	.14
Fatigue	55 (48.3)	11 (78.6)	.05
Feverish or chilly	35 (30.7)	6 (42.9)	.37
Headache	43 (37.7)	7 (50.0)	.40
Muscle pain	45 (39.5)	5 (35.7)	1.00
Nausea/vomiting	9 (7.9)	3 (21.4)	.13
Numbness or tingling	23 (20.2)	4 (28.6)	.49
Stiff neck	38 (33.3)	6 (42.9)	.55
Memory or concentration impairment	17 (14.9)	4 (28.6)	.25
Prolonged PR on EKG	2 (1.8) (out of n = 111)	2 (15.4) (out of n = 13)	.05

Data are no. (%).

Abbreviations: EKG, electrocardiogram; PR, time from the onset of the P wave to the start of the QRS complex; PTLDS, post-treatment Lyme disease symptoms.

Table 3. Characteristics of 14 Patients With Post-Treatment Lyme Disease Symptoms Prospectively Followed for 11–20 Years

Case No.	Age at Baseline (y)	Sex	EM	No. of Symptoms at Baseline	Persistent Symptoms[a]	Onset of Persistent Symptoms	Duration of Persistent Symptoms	Duration of Follow-up	Serology at Last Visit
1	50	M	S	3	Fatigue, cognitive	Baseline	Fatigue 15 y Cognitive 15 y	16 visits over 15 y	Reactive C6
2	54	F	S	5	Fatigue	Baseline	3 y	18 visits over 18 y	Negative C6
3	55	F	Mlt	4	Headache	Baseline	1 y	13 visits over 17 y	Negative C6
4	57	F	Mlt	5	Fatigue, cognitive, paresthesia/ numbness	Fatigue and cognitive at baseline paresthesia/ numbness after baseline visit	13 y	14 visits over 13 y	Reactive C6
5	40	F	S	7	Cognitive	Baseline	14 y	13 visits over 16 y	Negative C6
6	45	F	S	0	Cognitive, stiff neck, joint pains	After baseline visit	≤6 y	11 visits over 13 y	Not done
7	42	F	Mlt	7	Cognitive, stiff neck, joint pains, fatigue, headache	Baseline except cognitive	Variable; only cognitive lasted until year 18	7 visits over 18 y	Reactive WCS EIA
8	37	M	S	3	Fatigue	Baseline	1 y	14 visits over 19 y	Negative C6
9	49	M	Mlt	2	Paresthesia/ numbness[b]	After baseline visit	2 y	7 visits over 11 y	Negative C6
10	72	F	S	4	Fatigue, cognitive	Fatigue at baseline Cognitive after baseline	11 y	12 visits over 11 y	Negative C6
11	45	M	Mlt	9	Cognitive	Baseline	16 y	14 visits over 16 y	Negative C6
12	43	M	Mlt	6	Joint pain	Baseline	20 y	16 visits over 20 y	Reactive C6
13	55	M	S	8	Numbness[b]	Baseline	3 y	7 visits over 13 y	Negative C6
14	70	M	S	2	Balance problems[b]	Baseline	13 y	14 visits over 14 y	Negative WCS EIA

Abbreviations: EIA, enzyme immunoassay; EM, erythema migrans; Mlt, multiple; S, single; WCS, whole-cell sonicate.

[a] Cognitive indicates memory or concentration difficulties.

[b] Symptom may have been due to focal nerve injury.

the 114 other subjects (Table 1) indicates that there were no significant differences between these groups with regard to sex, age at the baseline visit, duration of illness until presentation, history of prior Lyme disease, seroreactivity by a first-tier antibody test to *B. burgdorferi* at the baseline or last visit, and duration of follow-up. There was a trend for patients with PTLDS to more likely have multiple EMs at the baseline visit—6 (42.9%) of 14 compared with 19 (16.7%) of 114 ($P = .03$)—and to have more symptoms at the baseline visit (mean ± SD = 4.64 ± 2.56 vs 3.28 ± 2.84; $P = .09$).

In comparing the frequency of 12 baseline symptoms between the 14 subjects with PTLDS and the other 114 subjects (Table 2), there was a trend for fatigue to have been reported more frequently among the PTLDS subjects (n = 11/14 [78.6%] vs n = 55/114 [48.3%]; $P = .05$). The PR interval at the baseline visit was also more often prolonged (ie, >200 milliseconds) in the PTLDS group (n = 2/13 [15.4%] vs n = 2/111 [1.8%]; $P = .05$).

Of the 14 subjects with PTLDS, 9 (64.3%) only had a single symptom, whereas the other 5 each had ≥2 symptoms, up to 5 symptoms (Table 3). The most common symptom reported by subjects with PTLDS was memory or concentration difficulties, present in 7 subjects, followed by fatigue in 6 subjects. Joint pain was reported by 3 subjects. An abnormal sensation that was localized to 1 or 2 anatomic sites was reported by 3 subjects, including 1 who had residual paresthesias at the site of the prior EM. Other symptoms included headaches in 2 subjects, stiff neck in 2 subjects, and feeling "off balance" in 1 subject. For the majority (ie, 12 subjects) at least 1 of the residual symptoms was noted at the baseline visit, and for the other 2, the symptoms developed within 3 months of the baseline visit. For only 6 of the subjects with PTLDS did the symptoms persist until the last follow-up visit. For the other 8 subjects, the documented duration of persistence of at least 1 symptom varied from 1 year to 14 years. One or more symptoms persisted for >10 years in 8 (57.1%) of the 14 subjects.

Table 4. Microbiologic Findings and Treatment of 14 patients With Post-Treatment Lyme Disease Symptoms Followed for 11–20 Years

Case No.	Skin Culture Result	Blood Culture Result	Baseline Treatment for Lyme Disease	Retreatment Directed at Persistent Symptoms	Recurrence of Erythema Migrans	Intercurrent Antibiotics Active Against *Borrelia burgdorferi* Prescribed for Other Reasons
1	RST3, OspC I	Neg	Doxy ×14 d	None	No	Yes
2	RST3, OspC M	Neg	1 dose CTX; Doxy ×10 d;	None	No	Yes
3	RST1 and RST2, OspC- nd	Neg	Doxy ×10 d	None	Yes at 2 y into f/u	Yes
4	RST3, OspC E	RST3, OspC E	Doxy ×14 d	None	Yes at 11 y into f/u	Yes
5	RST1, OspC B	RST1, OspC B	CTX ×8 d; Doxy ×14 d	Yes doxy ×28 d at 1 y	No	Yes
6	RST1, OspC B	Neg	Doxy ×14 d	Yes, twice with doxy during the first 6 mo	No	Yes
7	RST1, OspC A	Neg	Azithro ×7 d	Yes, twice- doxy ×14 d at 2 mo and CTX ×14 d at 1 y	No	Yes
8	RST3, OspC D	Neg	1 dose CTX; Doxy ×10 d	None	No	Yes
9	RST2, OspC K	Neg	Doxy ×14 d	None	No	No
10	RST1 and RST2, OspC- nd	RST1, OspC B	Doxy ×14 d	None	No	Yes
11	RST2, OspC K	RST2, OspC K	CTX ×4 d; Doxy ×14 d	Yes × multiple times	No	Yes
12	RST1, OspC nd	Neg	Amox ×20 d	None	No	Yes
13	RST3, OspC I	RST3, OspC I	Doxy ×14 d	None	No	No
14	RST1, OspC A	Neg	Doxy ×20 d	None	No	Yes

Abbreviations: Amox, amoxicillin; Azithro, azithromycin; CTX, ceftriaxone; Doxy, doxycycline; f/u, follow-up; nd, not done; Neg, negative; OspC, outer surface protein C; RST, ribosomal spacer type.

Comorbidities were common in study subjects, irrespective of whether they had PTLDS (Table 1). Of the 14 subjects with PTLDS, 8 had been hospitalized for non–Lyme disease-related medical conditions over the follow-up period. For the 6 subjects with persistent symptoms until the final visit, 5 of the 6 had had an intercurrent hospitalization for a surgical procedure.

For the 11 subjects with PTLDS who had a symptom severity score recorded at both the last visit and at the first visit that the symptom occurred, the mean ± SD score at the last visit was 2.89 ± 1.84 with a range of 0.3–6.6 based on a visual analogue scale (with possible scores of 0 to 8), compared with 3.35 ± 2.20 with a range of 0.6–7.1 ($P = .54$) at the first visit. Of the 6 subjects with a post-treatment Lyme disease symptom at their final visit, 4 were seroreactive (ie, positive or equivocal) by a first-tier serologic assay at that visit.

Of the 14 patients with PTLDS, none was considered to be functionally impaired because of PTLDS at their final study visit. Based on the first question on the SF-36v2 that 12 of the subjects with PTLDS completed, 9 (75%) characterized their health as good to excellent at that visit. Of the 3 subjects who

Table 5. Comparison of the 128 Subjects Able to be Followed for 11–20 Years vs the Other 155 Subjects Who Were Enrolled in the Study

Variable	Groups		*P* Value
	Subjects Who Were Followed ≥11 y	Subjects Who Were Followed for <11 y	
No.	128	155	
No. males (%)	71 (55.5)	103 (66.5)	.07
Mean age ± SD at study entry (median, range)	48.58 ± 11.57 (47, 25–76)	42.59 ± 13.31 (42, 16–75)	.0001
No. with multiple erythema migrans at study entry (%)	25 (19.5)	40 (25.8)	.26
No. symptomatic at study entry (%)	104 (81.3)	132 (85.2)	.42
Mean no. of symptoms at study entry ± SD (median, range)	3.41 ± 2.82 (3, 0–10)	4.33 ± 3.23 (4, 0–11)	.01
No. of patients with ≥6 symptoms at study entry (%)	33 (25.8)	48 (31.0)	.36
Mean no. of days of illness until baseline visit ± SD (median, range)	5.44 ± 6.69 (3, 0–42)	7.00 ± 8.46 (4, 0–66)	.09

Abbreviation: SD, standard deviation.

characterized their health as fair to poor at their final visit, 1 did not have any symptom associated with their PTLDS at that visit, and for the other 2 the level of severity of the post-treatment Lyme disease symptoms was 2.2 and 6.1 (out of a maximum of 8), respectively. The first subject of the latter 2 also had a number of serious comorbidities, including post-traumatic stress disorder and a colovesical fistula.

To investigate other possible predisposing factors for development of PTLDS, we assessed the genotypes of the infecting *B. burgdorferi* strains that were originally cultured from the study subjects (Table 4), but no pattern emerged that suggested that such symptoms are related to a specific strain of *B. burgdorferi*.

To evaluate for potential selection bias, we compared certain variables for the 128 subjects followed for >10 years with the other 155 subjects who entered the study but did not return at >10 years into follow-up (Table 5). Some differences were found. The 155 subjects who did not return at this time point were 6 years younger at study entry on average (mean ± SD of 42.59 ± 13.31 years vs 48.58 ± 11.57 years; $P < .001$) and had approximately 1 more symptom (mean ± SD of 4.33 ± 3.23 symptoms vs 3.41 ± 2.82 symptoms; $P = .01$). Among those not returning, men represented a greater proportion (66.5%; n = 103/155) compared with those who returned (55.5%; n = 71/128).

DISCUSSION

This study reports clinical and microbiological data on 128 culture-confirmed patients with early Lyme disease who were followed prospectively for 11–20 years after diagnosis. The findings expand upon our earlier publication in 2003 [3] while the study was in progress. The prior publication reported on the outcome at up to 9 years after enrollment and concluded that approximately 10% of subjects had PTLDS at their last visit, which was a mean of 5.6 years into follow-up [3].

The current analysis was based on the 128 subjects who followed up for 11–20 years. Overall, the study found that 14 (10.9%) experienced possible PTLDS after study entry. However, only 6 of the total (4.7%) had residual symptoms at the last follow-up visit. Although the findings show that such symptoms can persist for >10 years, this is not the situation for everyone with PTLDS. Of the 8 subjects whose symptoms apparently resolved before their last follow-up visit, 6 (75%) had symptoms that resolved within 10 years of follow-up.

In most cases, the symptoms that persisted were present at the baseline visit; in the others, symptom onset was typically within 3 months of the baseline visit. None of the 6 subjects with persistent symptoms at their last visit had evidence of functional impairment caused by the symptoms and thus did not meet criteria for post–Lyme disease syndrome [1]. For 5 of these 6 subjects who provided their own assessment of their overall health status at their last visit, 3 stated that their health was very good or good. The single individual who stated that his health status was poor had multiple comorbidities that likely contributed to this assessment as the visual analogue scale score for the single residual symptom (ie, difficulty concentrating) was only 2.2 out of a maximum value of 8.

Consistent with these results, in prior analyses of several other measures of health status in our prospective study, the health-related quality of life of the 100 individuals who were assessed by the SF-36v2 at their final study visit, including 5 of the 6 subjects with residual symptoms from PTLDS at that visit, was comparable with that of the general population [6]. In addition, the frequency of fibromyalgia at the last follow-up visit was only 1% in this group of 100 subjects [5], and all of the subjects in this group of 100 who had evidence of severe fatigue based on a score of >4.0 on the FSS-11 at this visit had causes other than PTLDS to explain their fatigue [4].

In our prior report [3], subjects with PTLDS were significantly more likely than those without PTLDS to have multiple EMs and to have had more symptoms on presentation. Similar trends were observed in this study, but statistical significance was not found. To investigate other possible predisposing factors for the development of PTLDS, we reviewed the genotypes of the strains of *B. burgdorferi* that caused the initial infection, but this analysis did not indicate a distinctive pattern that differed from our overall experience with the borrelial strains associated with EM [8]. A limitation of this analysis is the relatively small number of PTLDS cases assessable.

Another limitation of this study is that only 128 of the 283 subjects who entered the study were able to be followed up for >10 years, raising the possibility of selection bias. Indeed, the 155 subjects who did not return at this time point were an average of 6 years younger at study entry and had approximately 1 more symptom. The proportion of study subjects who were the most symptomatic at the baseline visit, with ≥6 symptoms, however, was comparable between those who were followed for >10 years and those who were not. Age at presentation did not affect the likelihood of persistent symptoms in a European study of patients with EM [9].

An additional study limitation is that the cause of the same symptom over time may have been different but still attributed to the prior episode of Lyme disease, as fatigue, memory or concentration difficulties, and joint pains are very common symptoms, have multiple potential etiologies, and often arise as an individual ages [10, 11]. In addition, 3 subjects were considered to have PTLDS in this analysis who may instead have had focal nerve injury from the original episode of Lyme disease rather than unexplained subjective symptoms. In addition, we only directly assessed whether PTLDS affected functionality for the 6 subjects with symptoms still present at their final visit.

Our study was not intended to determine whether retreatment with additional antibiotics may be beneficial for relieving persistent symptoms. Other studies have specifically addressed this issue but primarily for patients with post–Lyme disease syndrome rather than PTLDS as defined herein. These studies failed to provide convincing evidence of clinical benefit [12–15].

In summary, nonspecific symptoms in patients with culture-confirmed early Lyme disease may persist for up to 20 years in some cases. Such long-standing symptoms were not associated with functional impairment in this study.

Notes

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