Characterizing the Symptoms of Patients with Persistent Post-Treatment Lyme Symptoms: A Survey of Patients at a Lyme Disease Clinic in Rhode Island

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ABSTRACT

BACKGROUND: 10–20% of individuals diagnosed with Lyme disease develop chronic symptoms after antibiotic treatment.

METHODS: A convenience sample of adults with self-reported, persistent post-Lyme treatment symptoms seeking treatment at the Lifespan Lyme Disease Center in Rhode Island completed a demographic and medical survey, the Patient Reported Outcomes Measurement Information System (PROMIS)-29 v2.0, and other short-form PROMIS measures of cognitive function, sleep disturbance, and fatigue.

RESULTS: Compared to average standardized scale scores (T=50; SD=10), participants had mild impairments in physical (T=41) and social (T=42) functioning, mild symptoms of depression (T=56), anxiety (T=60), and sleep disturbance (T=57), and moderate pain interference (T=62), and fatigue (T=65). Participants reported greater symptoms than some other clinical samples including those with cancer and chronic pain. Post-hoc analyses revealed that women reported higher levels of fatigue than men.

CONCLUSIONS: People with persistent post-Lyme treatment symptoms report debilitating symptoms and functional impairments which must be considered in clinical care.

KEYWORDS: Lyme disease, chronic disease, patient-reported outcomes, quality of life

ABBREVIATIONS: α – Cronbach's alpha;
PROMIS – Patient-Reported Outcomes Measurement Information System;
PTLDS – post-treatment Lyme disease syndrome

BACKGROUND

Lyme is the most common vector-borne disease in the United States with an estimated 300,000 new cases each year, and Northeastern states, including Rhode Island, have particularly high rates of Lyme infection.[1] Among those who do undergo recommended antibiotic treatment for acute symptoms (e.g., distinct skin rash, fever, headache, muscle and joint aches), an estimated 10-20% develop symptoms of persistent fatigue, pain, and impaired cognitive functioning that persist more than 6 months post-treatment in the absence of continued clinical findings such as a rash.[2]

These persistent symptoms, known as post-treatment Lyme disease syndrome, or PTLDS, are distinct from the acute phase of Lyme disease and medically unexplained. The Infectious Diseases Society of America has proposed inclusion criteria for the diagnosis of PTLDS including a previous diagnosis of Lyme, stabilization of symptoms after antibiotic treatment, and relapsing symptoms of fatigue, musculoskeletal pain, or complaints of cognitive difficulties that persist for at least 6 months after completing antibiotic treatment. Risk factors for PTLDS have been identified (e.g., having more severe symptoms and being diagnosed at a later date),[3] but the etiology and pathophysiology are not well understood.[4] These persistent symptoms overlap with many other conditions including chronic fatigue syndrome and Epstein-Barr virus infection, which can lead to extensive diagnostic workups and may complicate and delay diagnosis causing confusion and uncertainty in the patient.[5] Limited understanding and support for PTLDS in the medical support may lead to conflict and strained communications between patients and providers, and patients have reported feeling dismissed and frustrated.[6]

At the same time, patients may be experiencing significant morbidity[6] and may report declines in functioning commensurate with patients with congestive heart failure.[7] Some patients with post-treatment Lyme disease symptoms feel hopeless about ever returning to their baseline (pre-Lyme) level of functioning.[6] Clinical trials have failed to demonstrate benefits of continued antibiotics for persistent symptoms[8], thus, clinical care for PTLDS generally consists of symptom management.[4]

Study Aims

The search is underway to develop appropriate diagnostic tests and treatments for PTLDS; but, in the meantime, patients are suffering with debilitating symptoms. The current proposal aims to explore the constellation and severity of these persistent, post-treatment Lyme disease symptoms. Our work can contribute to a better understanding of the types and severity of symptoms experienced by patients who reported having post-treatment Lyme disease symptoms.

METHODS

Setting and Sample

Patients were approached by a study team member during routine care at the hospital-affiliated, outpatient Lifespan Lyme Disease Center. Patients were eligible if they self-reported 1) being 18 years of age or older, 2) being a patient at the Center, and 3) self-reporting a history of Lyme disease with persistent symptoms that were present at least 6 months post-treatment and believed to be related to their Lyme diagnosis as based on the inclusion criteria proposed by the Infectious Diseases Society of America.[9]

Study Procedures

Patients were approached and provided with a brief description of the study. Interested patients were asked to self-report whether they met eligibility criteria. Eligible patients were then provided with a one-page patient information letter (written in English) that described the study purpose and procedures and elements of informed consent (e.g., voluntary nature of the study) and the survey packet. No identifying information was collected. Participants were compensated with a $10 gift card once they completed the surveys. All procedures were deemed to be exempt from federal regulation by the Lifespan Institutional Review Board Reference 207117 45CFR 46.101(2).

Measures

Surveys included a brief demographic and medical history survey that included gender and time since onset of symptoms.[4,10]

Symptoms were measured using the Patient-Reported Outcomes Measurement Information System (PROMIS®) and Cronbach's alpha (α) was calculated for each scale using the current sample:

1. PROMIS-29 Profile v2.0 assessed physical function (4 items; α=.913), anxiety (4 items; α=.922), depression (4 items; α=.931), fatigue (4 items; α=.950), sleep disturbance (4 items; α=.795), ability to participate in social roles and activities (4 items; α=.952), and pain interference (4 items; α=.974) and pain intensity (1 item),[11]
2. Neuro-QOL Item Bank v2.0 – Cognitive Function – Short Form assessed cognitive abilities such as attention, and concentration (8 items; α=.952),[12]
3. PROMIS Item Bank v1.0 – Fatigue – Short Form 7a measured additional fatigue-related concepts (7 items; α=.804),[13] and
4. PROMIS Item Bank v1.0 – Sleep-Related Impairment – Short Form 8a measured additional sleep-related concepts (8 items; α=.901).[14]

All PROMIS® measures use a 7-day recall period and relevant 5-point Likert scales (e.g., 1=never, 2=rarely, 3=sometimes, 4=often, 5=always). For each scale, scores are summed and converted to a standardized T-score with using conversion tables available in the scoring instructions at the PROMIS website. The standardized average was 50 with a standard deviation of 10. Higher scores mean more of the concept that is being measured. Here, higher scores on the physical function, social roles, and cognitive function (sub) scales indicate less functional impairment (i.e., better functioning) with standard benchmarks for mild (T = 40–45), moderate (T = 30–40), or severe (T < 30) impairment. Higher scores on the anxiety, depression, fatigue, seep disturbance, pain interference, and pain intensity indicate greater severity of symptoms with standard benchmarks for mild (T = 55–60), moderate (T= 60–70), and severe (T > 70) symptoms. Possible ranges for total raw (sub)scale scores were 4–20 for the subscales of the PROMIS-29 measure (with the exception of pain intensity which consists of a single item rated on an 11-point Likert scale from 0 for 'no pain' to 10 for 'worst pain imaginable'), 8–40 for the 8-item cognitive function and sleep-related impairment short forms, and 7–35 for the 7-item fatigue short form.

Data Analysis

Raw data was entered in IBM SPSS Statistics 20 and scale scores were calculated per PROMIS scoring instructions. Cronbach's alpha (α) was calculated to measure internal consistency for each scale within the current sample. Frequencies and percentages were calculated for all demographic and medical variables, and means and standard deviations were calculated for all (sub)scale scores. Pearson correlations were calculated between all (sub)scales. PROMIS Raw scale scores were converted to T-scores using the PROMIS T-score conversion tables to allow for comparison between our sample, the reference sample on which the scores were normalized, and other patient groups that have been assessed using PROMIS scales. Finally, average (sub)scale scores were compared by gender (male or female), age group (18–30, 31–50, 51–70), and time since onset of post-treatment Lyme disease symptoms (<1 year, 1–3 years, 4+ years) utilizing analysis of variance.

RESULTS

Fifty-two (N=52) patients provided demographic and medical history information (see **Table 1**) and completed PROMIS® measures. All PROMIS (sub)scales were significantly correlated, most at the .01 p-value level. Patients in this sample reported symptoms that were generally 0.5-1.0 standard deviations more severe and impaired than not only the PROMIS reference sample, but also clinical samples including those with cancer and chronic pain (see **Table 2**).

Compared to the reference sample (T=50; SD=10), patients with persistent symptoms had mild impairment in physical (T=41) and social (T=42) functioning, mild symptoms of depression (T=56), anxiety (T=60), and sleep disturbance (T=57), and moderate symptoms of pain interference (T=62), and fatigue (T=65).

Table 1. Demographic and Medical Variables (n=52)

	n (%)
Gender	
Male	23 (44.2)
Female	29 (55.8)
Age (years)	
18–30	12 (23.1)
31–50	16 (30.7)
51–70	24 (46.2)
Time Since Onset of Symptoms	
Less than 6 months	4 (7.7)
6–12 months	8 (15.4)
1–3 years	20 (38.5)
4–10 years	8 (15.4)
More than 10 years	12 (23.1)
Positive Lyme Serology	49 (96.1)
Immunoglobulin M antibodies	14 (27.5)
Immunoglobulin G antibodies	16 (31.4)
Not Sure	29 (56.9)
Co-Morbid Conditions (current or past)	
Lyme Rash	21 (45.7)
Bell's Palsy	8 (18.6)
Arthritis	33 (70.2)
Heart Disease	7 (16.3)
Neurological Disease	19 (44.2)

Table 2. PROMIS® (sub)scale means (standard deviations [SDs]) and T-scores for the study sample, as well as T-scores for the reference sample and other published samples of patients with chronic health conditions

	Study Sample		T-scores for Reference and Other Published Samples			
	Study Sample Mean (SD)	Study Sample T-scores	Reference Sample	Neuro-Endocrine Tumors (26)	Systemic Scleroderma (27)	Musculo-Skeletal Pain (28)
Physical Function	13.92 (4.22)	41	50	45	47	41
Anxiety	10.81 (4.42)	60	50	54	50	52
Depression	9.40 (4.62)	56	50	52	49	50
Fatiguea	15.90 (3.90)	65	50	55	52	54
Sleep Disturbancea	13.53 (3.34)	57	50	52	52	52
Social Roles	10.94 (4.40)	42	50	46	48	45
Pain Interference	13.06 (4.94)	62	50	52	55	61
Pain Intensity	5.63 (2.44)	N/A	N/A	N/A	N/A	N/A
Cognitive Function	24.52 (8.46)	40	50	N/A	N/A	N/A
Fatigue SF-7ab	24.71 (4.64)	63	50	N/A	N/A	N/A
Sleep SF-8a	26.77 (6.80)	62	50	N/A	N/A	N/A

[a] n=51; [b] n=48

There were no significant or trending differences in average (sub)scale scores by age, but there were differences in subgroup comparisons. Specifically, women reported greater levels of fatigue than men on both the fatigue subscale of the PROMIS-29 (mean = 17.36 [SD = 2.45] versus 14.13 [4.60]; $F[1,49]=10.24$, $p<.01$) and the PROMIS Fatigue-SF 7a (26.21 [4.29] versus 22.60 [4.36]; $F[1,46]=8.18$, $p<.01$). Scales scores also varied by time since onset of post-treatment Lyme disease symptoms such that those who reported such symptoms for <1 year had the greatest average total scores for fatigue and sleep disturbance (see **Table 3**). No other significant differences were found.

DISCUSSION

Relevant patient-reported outcomes were assessed among individuals with self-reported post-treatment Lyme disease symptoms who were seeking care at The Lifespan Lyme Disease Center in Rhode Island. Fatigue and pain were the most highly endorsed symptoms, though the patients in this sample reported symptoms and functional impairments that were more severe than both the general population and other severely and chronically ill groups of patients such as cancer and chronic pain.[15-17] Though the mean anxiety score was relatively low, that translated to a relatively high anxiety T-score, suggesting that anxiety levels endorsed in this group were quite a bit higher than the comparison groups.

Differences in symptoms scale scores were examined by gender, age group, and time since the onset of the post-treatment Lyme disease symptoms. Significant differences emerged in terms of fatigue and sleep disturbance such that women reported greater levels of a fatigue, and those who had been diagnosed for the shortest amount of time (less than 1 year) reported the greatest levels of fatigue and sleep disturbance. Gender differences are in line with other evidence that suggests that fatigue is more commonly reported by women than men.[18] In terms of the duration of symptoms, it is not uncommon to see fluctuations in symptoms over the course of an illness. For example, many patients with chronic fatigue syndrome – a condition that is similar to post-treatment Lyme disease syndrome – report fluctuating symptom severity and lower prevalence of fatigue over time.[19]

Table 3. Subgroup comparisons of average PROMIS® (sub)scale scores between participants identifying as male or female, and time since onset of symptoms (<1 year, 1–3 years, 4+ years)

	Grouping Variable	Levels	Mean (SD)	F Statistic (df)	P Value	Observed Power
PROMIS-29 Fatigue	Gender	Male Female	14.13 (4.60) 17.36 (2.45)	10.24 (1,49)	.002	0.88
	Time Since Onset	<1 year 1–3 years 4+ years	17.36 (3.38) 14.35 (4.57) 16.65 (2.96)	2.94 (2,48)	.063	0.55
PROMIS-29 Sleep Disturbance	Gender	Male Female	12.96 (3.25) 14.00 (3.40)	1.24 (1,49)	.272	0.19
	Time Since Onset	<1 year 1–3 years 4+ years	15.58 (2.81) 12.15 (3.52) 13.68 (2.85)	4.56 (2,48)	.015	0.75
PROMIS-SF Fatigue	Gender	Male Female	22.60 (4.36) 26.21 (4.29)	8.18 (1,46)	.006	0.80
	Time Since Onset	<1 year 1–3 years 4+ years	27.50 (4.40) 22.94 (5.13) 24.90 (3.65)	3.46 (2,45)	.040	0.62
PROMIS-SF Sleep-Related Impairment	Gender	Male Female	24.78 (7.48) 28.34 (5.86)	3.71 (1,50)	.060	0.47
	Time Since Onset	<1 year 1–3 years 4+ years	30.92 (5.82) 23.45 (7.69) 27.60 (4.71)	5.63 (2,49)	.006	0.84

LIMITATIONS

The study limitations should be considered when interpreting these findings. This study consisted of a small convenience sample of patients who – in the absence of diagnostic testing for PTLDS – self-identified as having post-treatment symptoms associated with Lyme diseases. Of note, 96% did report having a positive Lyme serology. Additionally, scale comparisons by gender, age, and time since onset of symptoms were underpowered and should be considered exploratory analyses only. Given that the diagnosis and treatment of post-treatment Lyme disease syndrome or chronic Lyme can be contested among medical professionals and confusing for patients, our sample may have included a relatively heterogenous sample. Future studies should consider the feasibility of confirming diagnosis per medical record.

IMPLICATIONS FOR CLINICAL PRACTICE

The symptoms endorsed by the participants in this study including fatigue, pain, sleep disruption, and issues with cognitive function are similar to those seen in conditions such as chronic fatigue syndrome.[5] Without any clear diagnostic testing for these three conditions with similar clinical presentations, consideration of a PTLDS diagnosis will rely on the collection of medical history information pertaining to Lyme disease. Relevant medical history includes whether and when the participant had any symptoms of Lyme disease (e.g., characteristic Lyme rash), has had a prior positive Lyme serology, and if the participant received treatment for diagnosed or presumed Lyme infection. Additionally, clinicians should consider that patient characteristics may affect their symptom profile. For example, while limited in scope, this study replicates previous findings[18] that women report higher levels of fatigue than men, which may influence diagnostic and treatment considerations.

IMPLICATIONS FOR FUTURE RESEARCH

Prospective studies that begin following patients around the onset of symptoms, assess pre-morbid functioning as close in time to the onset of symptoms as possible, and monitor symptoms across months or years are warranted. To our knowledge one such study exists to date, but only followed patients out 6 months after acute Lyme infection.[4] These prospective studies should assess symptoms in concert with disease-specific events (e.g., biomedical or other treatments), comorbid medical conditions and treatments, and other life events. In addition to long-term symptom monitoring, previous work has suggested diurnal fluctuations in symptoms such as fatigue.[20] Future studies should employ methods intended to take frequent, real-world assessments of symptoms such as ecological momentary assessment and actigraphy.

CONCLUSIONS

While many patients recover from acute Lyme infection after antibiotic treatment, there is a sizeable group of patients who continue to experience symptoms including fatigue, pain, and cognitive disruptions for months or years after initial treatment.[2] These patients report severe morbidity, with life-changing disruptions to their physical, cognitive, emotional, and social functioning.[6-8] With little known pathophysiology,[4] and no diagnostic testing for post-treatment Lyme disease symptoms,[5] accurate diagnosis and assessment and management of symptoms is critical to improving daily functioning and quality of life. Identifying the most disabling, persistent Lyme symptoms will also aid in assessing the effects of therapeutic interventions or symptom management approaches. This work contributes to efforts to better understand persistent symptoms following Lyme diagnosis and treatment and suggests a number of clinical and research questions to be addressed in future studies.

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