Characterizing Post-treatment Lyme Disease Syndrome: A Mixed Methods Study of Patients at a Lyme Disease Clinic in Rhode Island

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ABSTRACT

BACKGROUND: Mixed quantitative and qualitative research methods may be useful for characterizing the experiences of patients with post-treatment Lyme disease syndrome.

METHODS: 15 participants completed demographic and screening questions, surveys assessing quality of life, fatigue, pain, cognitive functioning, and other patient-reported outcomes, a semi-structured in-depth interview, and consented to a Lyme-related medical chart review.

RESULTS: Participants reported mild to moderate symptoms and functional impairments on patient-reported outcome surveys and in-depth interviews. Participants reported on a number of management strategies that they found more or less effective in managing their symptoms. Participants endorsed the need for better clinical assessment of symptom patterns over time, greater Lyme-related education for providers, more holistic approaches to diagnosis and care, and the desire to participate in Lyme-focused support groups.

CONCLUSIONS: Overall, participants desired a more holistic approach to diagnosis, symptom assessment, and symptom management. Recommendations for future research and clinical considerations are discussed.

KEYWORDS: post-treatment Lyme disease, mixed methods, patient-reported outcomes, quality of life

INTRODUCTION

The Centers for Disease Control and Prevention (CDC) estimate that approximately 476,000 people are diagnosed with Lyme disease in the United States (US) each year,[1] and Rhode Island is considered a high incidence state.[2] While most acute cases of Lyme disease resolve after 2–4 weeks of antibiotic treatment, an estimated 10-20% of those who undergo treatment experience persistent, debilitating symptoms including fatigue, pain, and impaired cognitive functioning at least 6 months post-treatment – a condition known as post-treatment Lyme disease syndrome, or PTLDS.[3-6] Recent estimates indicate that 2020 prevalence for PTLDS may be in the range of 1.6 to 2.3 million cases in the US.[7]

Our previous work has investigated clinical care at the Lifespan Lyme Disease Center in Providence, RI, using chart review and brief symptom surveys.[8-9] The current study employed mixed (i.e., quantitative and qualitative) methods to conduct an in-depth evaluation of 1) PTLDS symptom severity and symptom patterns, 2) which symptom assessment surveys, or survey items, are most relevant for PTLDS patients, and 3) patient recommendations for clinical care of PTLDS. This study aims to advance the science by using participatory methods to engage patients in improving assessment and care of PTLDS.

METHODS

Setting and Sample

Adult patients at the Lifespan Lyme Disease Center with a history of post-treatment symptoms (e.g., pain, fatigue, cognitive disruption) for greater than 6 months after at least 14 days of antibiotic treatment for diagnosed Lyme infection by either erythema migrans rash, Bell's palsy, or positive Lyme serology as based on the inclusion criteria proposed by the Infectious Diseases Society of America.[10]

Study Procedures

Interested individuals were screened by phone and eligible patients were scheduled for the one-time, in-person study visit inclusive of written informed consent and medical record release. Participants then completed paper symptom surveys and a semi-structured in-depth interview. Study visits, including the in-depth interview, were conducted by either the principal investigator or project director, both of whom have years of training and experience with mixed methods data collection, and neither of whom are involved in clinical care at the Center. Participants received $60 compensation for study activities completed during the approximately 2-hour, in-person study visit. All procedures were approved by the Miriam Hospital Institutional Review Board 205918 45 CFR 46.110(7).

Measures

Data collection included demographic (e.g., age and gender) and screening questions, symptom surveys, semi-structured interview questions, and Lyme-related medical history obtained from the patient's medical record.

Short Form (SF)-36

The SF-36 includes eight subscales which assesses various

general aspects of quality of life: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. Higher scores represent higher quality of life in the specific domain.[11] The SF-36 has been used in prior studies of PTLDS,[4,6] and the Cronbach's alphas varied from .718 to .962 in the current sample.

Fatigue Severity Scale (FSS)

The FSS nine-item scale assesses the effects of fatigue on daily functioning as secondary to other medical conditions.[12] The Cronbach's alpha in the current sample was .952.

Patient-Reported Outcomes Measurement Information System (PROMIS®)

The following PROMIS scales were administrated to each participant (**See Appendix A**): PROMIS-29 Profile v2.1, Neuro-QOL Item Bank v2.0 – Cognitive Function – Short Form, PROMIS Item Bank v1.0 – Fatigue – Short Form 7a, PROMIS Item Bank v1.0 – Pain Intensity – Scale, PROMIS Item Bank v1.0 – Pain Interference – Short Form 6a, and PROMIS Item Bank v1.0 – Sleep-Related Impairment – Short Form 8a.

Medical Record

Lyme-related information was extracted from each participant's medical record including 1) earliest positive Lyme serology date, 2) criteria upon which the Lyme diagnosis was made (e.g., erythema migrans rash, Bell's palsy, positive Lyme serology), 3) documented Lyme-related symptoms, 4) number and length of antibiotic cycles, and 5) whether there was a documented or suspected diagnosis of PTLDS.

In-Depth Interview

Each interview was guided by a semi-structured agenda focused on addressing the aims of the study and allowing flexibility to follow-up on participant responses and explore emergent themes. Participants were asked to describe symptoms and elaborate on the effects of PTLDS on well-being and psychosocial functioning. Participants were asked to provide feedback on the symptom surveys and whether they adequately and comprehensively capture their PTLDS experiences. Participants were also asked to share effective and ineffective symptom management strategies.

Data Analysis

Raw data was entered in IBM SPSS Statistics 20 and scale scores were calculated per established scoring instructions. Cronbach's alpha (α) was calculated to measure internal consistency for each scale within the current sample (**See Measures**). Frequencies and percentages were calculated for demographic and medical variables and means and standard deviations were calculated for all (sub)scale scores. PROMIS raw scale scores were converted to T-scores using the PROMIS T-score conversion tables to allow for comparison between our sample and the calibration sample on which the scores were normalized.

RESULTS

Quantitative Findings

Average participant age was 60.87 years, and the majority of participants were white women (**See Table 1**). Participants reported mild to moderate symptoms and functional impairments on all study measures (**See Appendix A**).

Table 1. Demographic and medical variables (N=15)

	Mean	Standard Deviation
Age	60.87	12.88
	Frequency	**Percentage**
Gender		
Female	10	67%
Male	5	33%
Race/Ethnicity		
White	14	93%
Black	0	—
Asian	1	7%
Latinx	0	—
Criteria for Lyme Diagnosis		
Known Tick Exposure	5	33%
Erythema Migrans Rash	5	33%
Facial Palsy	2	13%
Joint Swelling	3	20%
Positive Serology	13	87%
Enzyme Immunoassay (EIA)		
Positive	11	73%
Equivocal	1	7%
Immunoblots		
Immunoglobin M (IgM) only	5	33%
Immunoglobin G (IgG) only	4	27%
IgM + IgG	3	20%
Documented Antibiotic Cycles		
1 cycle	4	27%
2 cycles	6	40%
3 cycles	4	27%
4 cycles	1	7%
Longest Documented Antibiotic Cycle		
< 21 days	1	7%
21 days	2	13%
28 days	9	60%
>28 days	2	13%
Documented Symptoms		
Fever	0	—
Headache	4	27%
Fatigue	13	87%
Lyme Carditis	0	—
Muscle Aches	8	53%
Joint Pain	12	80%
Dizziness	1	7%
Cognitive Difficulties/"Brain Fog"	6	40%
Depression and/or Anxiety	4	27%
Documented Lyme-Related Diagnosis		
Post-Treatment Lyme Disease	14	93%
Diagnosed	12	80%
Suspected	2	13%
Antibiotic-Refractory Lyme Arthritis	1	7%

Qualitative Findings

Lyme Diagnosis

While two participants described satisfaction with their initial Lyme diagnosis because their provider was quick to recognize that their symptoms and request Lyme serology tests, most noted that their diagnosis of acute Lyme infection was delayed. Providers diagnosed or suspected a variety of non-Lyme-related medical conditions including fibromyalgia, contact dermatitis, anemia, unbloomed shingles, stroke, and depression before the patient arrived at a Lyme diagnosis. Three participants said their symptoms were believed to be due to aging, though participants doubted that their sudden onset of symptoms could be explained by a process like aging, which they believed would feel more gradual in nature. Five participants reported that they had to advocate for Lyme testing with resistant providers and/or for a sufficient (i.e., 21 day) course of antibiotics. Participants reported being referred to multiple specialists for specific symptoms including rheumatologists, neurologists, otolaryngologists, ophthalmologists, and chiropractors.

Symptoms and Functional Impairments

Fatigue and joint and other musculoskeletal (e.g., neck, back, leg) pain were frequently cited as the most severe and disruptive symptoms. Difficulty concentrating and "brain fog" were reported by many participants. Other symptoms reported by fewer participants included dizziness and vertigo, heart palpitations, temperature sensitivity, night sweats, and numbness in hands. Three participants reported difficulty sleeping due to pain and three others reported non-restorative sleep.

Participants reported a wide variety of functional impairments since their Lyme diagnosis. Five participants were no longer able to work or volunteer even though they would like to, and one had reduced their work hours, due to their symptoms. Most had reduced their social commitments, spending less time with friends, going out less with their spouse, and finding it difficult to commit to social activities. All participants reported that they had reduced or stopped engaging in at least some physically demanding activities because of pain or fatigue brought on by physical activity. Some participants differentiated between things that they had stopped doing (e.g., traveling, vigorous exercise, hiking) and things they still did but struggled through (e.g., driving, house and yard work, caring for grandchildren). Two participants stated that they actively avoid areas where they previously frequented (i.e., the woods, their yard) because they are concerned about exposure to Lyme.

Multiple symptom time courses were described. First, most participants noted how active and healthy they were prior to their Lyme infection, and how difficult it was to now struggle with completing the work, chores, and outdoor activities that they previously enjoyed. Second, participants noted fluctuations in their symptoms from day to day (i.e., good days and bad days) and over the course of weeks and months since their Lyme infection. Finally, participants reported consistent diurnal patterns such that they are most energetic and least fatigued upon waking in the morning, tire quickly through the day, and are "exhausted" by late afternoon or evening, with four participants frequently taking daytime naps to recover from exhaustion.

Symptom Management

Participants listed a variety of medical, alternative, and lifestyle approaches to managing their symptoms. Many took over the counter or prescription analgesics to manage pain and arthritis including ibuprofen, acetaminophen, hydrocodone-acetaminophen, steroid injections, trolamine salicylate cream, diclofenac, methotrexate, CBD oil, and medical marijuana. These medications offered some relief, with some participants noting that they "take the edge off" the pain or discomfort, and many participants reported continuous daily use of aspirin, ibuprofen, and pain-relieving creams. Three participants reported taking melatonin or a prescription medication to improve sleep. Most participants reported mixed efficacy of continued antibiotic treatment for PTLDS, with at least three participants clearly outlining how symptoms improve temporarily then resurface following each antibiotic cycle. One participant specifically identified antibiotics as a symptom management strategy, while at least one other participant noted that prolonged and repeated use of antibiotics is not recommended by the CDC and another suggested more information is needed on how antibiotics affect the gut.

Of the four people who had tried physical therapy, all four stated that it did not help, with one stating that it made their pain and symptoms worse. Participant's evaluation of exercise for symptom management was mixed. On the one hand, physical activity can cause participants to become extremely fatigued and weak, and thus all participants were less active than they were prior to their Lyme infection. On the other hand, some reported that getting exercise helped them feel better mentally, with one participant noting that at least after a walk, they had a reason to be exhausted. Ongoing exercise typically consisted of walking, or activities like meditation or yoga. One participant recommended a fitness tracking watch for external motivation to move more. With a few exceptions, sleep was generally restorative, with most participants having more energy and less fatigue upon waking in the morning or after a daytime nap. Participants described modifying their schedules to take advantage of the time earlier in the day when they have more energy. Two participants recommend heating pads for pain.

Most participants mentioned a dietary intervention, including keto, Mediterranean, and specific foods – like cinnamon or turmeric – meant to reduce inflammation. Of those who mentioned dieting as a potential symptom management strategy, most were either considering a dietary

change or making small changes, while two were skeptical and unlikely to adopt major diet changes. Most of the participants mentioned taking some type of supplement including magnesium, ginseng, and health shakes, which were regarded as moderately effective in improving symptoms like joint pain and concentration.

Other approaches included attending a detox spa, reiki massage, and a shaman healer. The spa and healer were perceived as moderately effective in improving symptoms, while the participant who mentioned reiki did not find it helpful. One participant was interested in possibly exploring the use of a rife machine. Another participant stated that she had no interest in interventions that did not have scientific evidence of effectiveness.

Symptom Assessment

Generally, participants felt that the survey items were relevant to their experiences with PTLDS, especially the fatigue scales. In fact, several participants reflected on a feeling of validation that came from seeing the types of symptoms that researchers were measuring in patients with PTLDS. Participants recommended site-focused, rather than general, pain questions (e.g., joint pain, neck pain). In terms of functional items, one participant preferred the term "interfered" to "limited" since they continued to engage in the activities even when they were difficult or uncomfortable. Others suggested additions included items assessing dizziness, temperature sensitivity (e.g., hot head, hot feet), night sweats, nightmares, visual impairments, and perceived level of support from healthcare providers.

Participants noted that fluctuations in symptoms overtime and throughout the day made it difficult to answer some questions, with one participant noting that it was unclear if we wanted responses based on a "good" or "bad" day so they averaged it. One participant noted that they would like more opportunity to express how their fatigue and pain changes over the course of a single day. Three participants suggested questions related to pre-Lyme functioning, including an assessment of activities that the patient is no longer doing, but would like to be doing.

Most participants said they would be happy to complete questionnaires regularly (e.g., at each clinic appointment, either at the clinic or prior to the appointment), and that they would be interested in seeing their scores compared to others with PTLDS, as well as changes to their symptom ratings over time as they utilize different symptom management strategies. One participant noted that we should keep the surveys brief and focused, given the concentration issues among patients with PTLDS, and that the providers can use the surveys as a starting point for a one-on-one conversation in the clinic room.

Clinical Care Recommendations

Participants wanted more education: for providers, for patients, and for the general public. For providers, participants focused on educating providers on how to recognize the constellation of Lyme symptoms and be more willing to test for Lyme early, before referring patients to a variety of specialists or assuming the symptoms are a result of aging. Some participants argued that if providers were to assess their pre-Lyme functioning and lifestyle, they would understand the sudden onset of symptoms that the patients do not believe to be related to the process of aging. One participant recommended a decision checklist for providers to identify when it was appropriate to order Lyme serology. Another participant warned against relying exclusively on the blood test (when they can be equivocal or inconclusive) and paying attention to the symptoms. One participant wanted providers to know about PTLDS specifically, so they would not be under the impression that every patient makes a full, sustained recovery after antibiotic treatment for the acute Lyme infection. One participant referred to PTLDS as a "lonely disease," and was among several others who wanted more peer interaction in the form of support groups or meditation classes.

DISCUSSION

The symptom cluster of fatigue, pain, and disruptions in cognitive function (namely, difficulty concentrating and "brain fog") continues to be well-documented in the PTLDS literature, as does perceived delays in Lyme-related diagnosis and feeling dismissed or misunderstood by medical providers.[4,6] In this sample, participants reported few sleep-related problems. While some participants took melatonin or other sleep aids, and some noted that pain would sometimes interfere with their sleep, most reported that sleep was relatively restorative and few endorsed high levels of sleep disturbance on the PROMIS scales. Real-time assessment of sleep and symptoms, such as actigraphy and ecological momentary assessment, may help to clarify if and how sleep is related to fatigue and pain, and whether sleep-focused interventions may be beneficial despite sleep disturbances not necessarily presenting as a primary complaint.

Observationally, many participants arrived at the study visit with an accounting of the course of Lyme disease and other co-morbid conditions in the form of electronic or paper notes or logs. Many patients tracked doctor's appointments, testing, antibiotic treatment, and symptom management attempts and outcomes. In their narratives and their actions, participants were eager for information. Some felt validated by the questions in the symptom surveys, and some wanted to fill out the surveys more regularly. The effect of symptom tracking on symptom management and Lyme-related health outcomes is a phenomenon worth further study.

The critical nature of assessing pre-morbid functioning and opportunities for exposure were other major themes to emerge from this data. Participants were clear that the precipitous symptom increases and declines in functioning were too drastic to be related to aging or any other more gradual process. Overall, prior to Lyme, these participants

were active people who enjoyed being outdoors, thus, providing many opportunities for Lyme exposure.

LIMITATIONS

Our sample size of 15, while sufficient for qualitative saturation in this sample, is too small to power any meaningful statistical comparisons between the samples. While psychometrically sound instruments were selected, scale findings are intended to be interpreted along with the qualitative data to generate hypotheses for future PTLDS symptom assessment and management in research and clinical settings. Additionally, given the homogeneity of participants in this sample, future work must strive to incorporate feedback from Hispanic/Latinx and non-White participants including employing inclusive recruitment and retention strategies as appropriate.

CONCLUSION

This in-depth exploration of the experiences of PTLDS patients at an outpatient Lyme clinic confirmed previous findings, while adding novel and critical details about how best to assess and clinically manage symptoms. Future research and clinical practice can incorporate the input and suggestions from patient with the ultimate goal of improving patient satisfaction, reducing symptoms, and improving health and well-being.

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Disclaimer

The views expressed herein are those of the authors and do not necessarily reflect the views of Lifespan or Brown University.

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Disclosures

Ethics Approval and Consent to Participate: This study was subject to expedited ethical review by The Miriam Hospital Institutional Review Board (Board Reference # 205918 45CFR 46.110(7)).

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