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CLINICAL RESEARCH ARTICLE

Pediatric Lyme disease: systematic assessment of post-treatment symptoms and quality of life

Maureen Monaghan[1,2], Stephanie Norman[3], Marcin Gierdalski[2,3,4], Adriana Marques[5], James E. Bost[2,3,4] and Roberta L. DeBiasi[2,3,6,7]✉

BACKGROUND: Lyme disease is common among children and adolescents. Antibiotic treatment is effective, yet some patients report persistent symptoms following treatment, with or without functional impairment. This study characterized long-term outcome of pediatric patients with Lyme disease and evaluated the case definition of post-treatment Lyme disease (PTLD) syndrome.

METHODS: The sample included 102 children with confirmed Lyme disease diagnosed 6 months—10 years prior to enrollment (M = 2.0 years). Lyme diagnosis and treatment information was extracted from the electronic health record; parent report identified presence, duration, and impact of symptoms after treatment. Participants completed validated questionnaires assessing health-related quality of life, physical mobility, fatigue, pain, and cognitive impact.

RESULTS: Most parents reported their child's symptoms resolved completely, although time to full resolution varied. Twenty-two parents (22%) indicated their child had at least one persistent symptom >6 months post-treatment, 13 without functional impairment (PTLD symptoms) and 9 with functional impairment (PTLD syndrome). Children with PTLD syndrome had lower parent-reported Physical Summary scores and greater likelihood of elevated fatigue.

CONCLUSIONS: In the current study, most children with Lyme disease experienced full resolution of symptoms, including those who initially met PTLD syndrome criteria. Effective communication about recovery rates and common symptoms that may persist post-treatment is needed.

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IMPACT:

- The majority of pediatric patients treated for all stages of Lyme disease reported full resolution of symptoms within 6 months.
- 22% of pediatric patients reported one or more symptom persisting >6 months, 9% with and 13% without accompanying functional impairment.
- Effective communication with families about recovery rates and common symptoms that may persist post-treatment of Lyme disease is needed.

INTRODUCTION

Lyme disease, caused by *Borreliella* (*Borrelia*) *burgdorferi* and transmitted by the bite of the ticks of the *Ixodes ricinus* complex, is the most common vector-borne disease in the United States and Europe.[1] Approximately 476,000 cases of Lyme disease are diagnosed and treated each year in the US,[2,3] with peak incidence in children 5–9 years of age.[4] Antibiotic treatment is effective for most patients, but some patients report persisting or relapsing nonspecific symptoms after treatment.[5]

These symptoms are referred to as post-treatment Lyme disease (PTLD) symptoms or syndrome, depending on their severity and functional impact,[6] following the Infectious Diseases Society of America (IDSA) proposed research case definition.[7] To fulfill criteria for PTLD symptoms, patients must have a documented episode of Lyme disease, received treatment with an accepted antibiotic regimen with resolution or stabilization of objective manifestation(s) of Lyme disease, report persistent or relapsing non-specific symptoms for at least a 6-month period post-antibiotic therapy, and have no other condition(s) that explain the symptoms. Symptoms need to cause a substantial reduction in previous levels of activity to be classified as PTLD syndrome.

PTLD syndrome is poorly understood in adults, with few studies attempting to operationalize its case definition,[6,8] and even less well-characterized in children. Mechanisms driving these symptoms and continued impairment are unknown and may differ in individual patients,[9–11] with more studies needed.[5,12] Risk factors

[1]Divisions of Psychology and Behavioral Health, Washington, DC, USA. [2]Department of Pediatrics, The George Washington University School of Medicine and Health Sciences, Washington, DC, USA. [3]Center for Translational Research, Children's Research Institute, Washington, DC, USA. [4]Division of Biostatistics and Study Methodology, Childrens National Research Institute, Washington, DC, USA. [5]Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA. [6]Division of Pediatric Infectious Diseases, Children's National Hospital, Washington, DC, USA. [7]Department of Microbiology, Immunology and Tropical Medicine, The George Washington University School of Medicine, Washington, DC, USA. ✉email: rdebiasi@childrensnational.org

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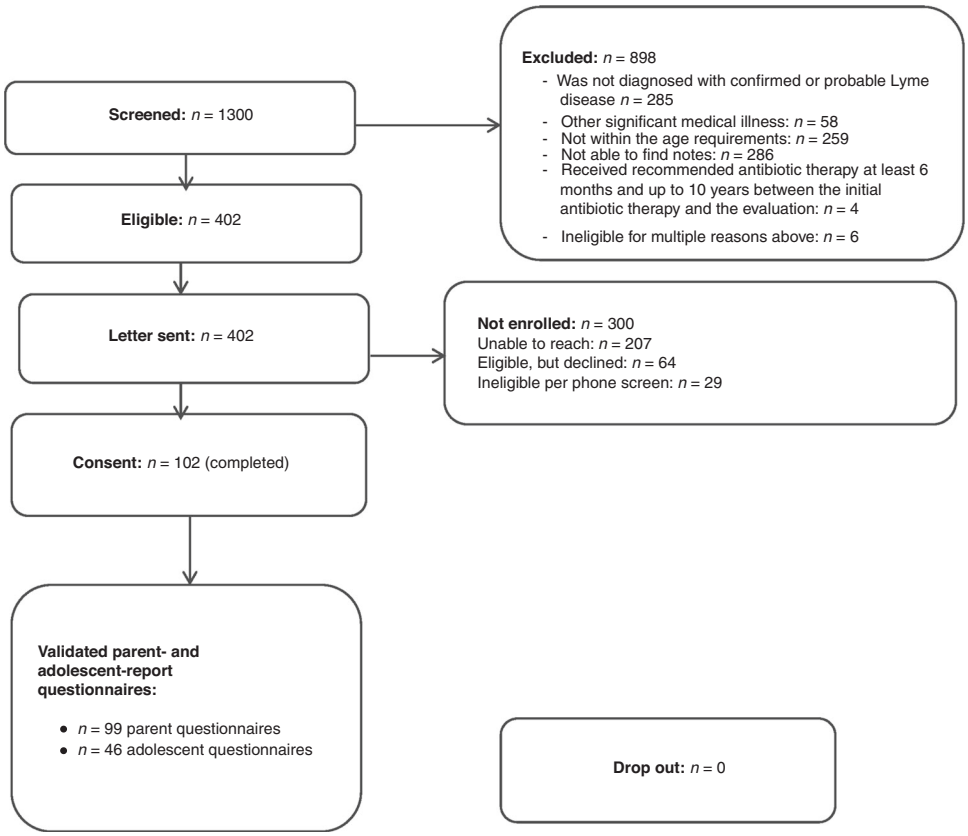

Fig. 1 Study CONSORT Table.

for persistent symptoms include illness severity at presentation, initial timing of antibiotic therapy, presentation with non-erythema migrans manifestations,[13–17] presence of comorbidities unrelated to Lyme disease,[18] older age, and female sex.[15,19]

While children are less likely to develop prolonged symptoms following Lyme disease,[20–26] there can be significant parental stress when there are lingering non-specific symptoms. Data regarding time to recovery and prevalence and characteristics of symptoms after treatment of Lyme disease in children may aid communication between clinicians, parents, and patients.[27]

The objective of this study was to characterize the long-term outcome of pediatric patients with Lyme disease through a cross-sectional evaluation using validated assessments of parent- and adolescent-reported outcomes, and to explore these assessments to operationalize the case definition of PTLD syndrome in this population.

METHODS

Participants

This cross-sectional study enrolled pediatric patients with a confirmed diagnosis of Lyme disease meeting current diagnostic criteria[28] at least 6 months and up to 10 years prior. Parents/guardians (hereafter parents) of children ages 5–18 years and adolescents ages 10–18 years were invited to participate in this single timepoint validated survey study. Potentially eligible participants were identified using ICD-9/ICD-10 diagnostic codes for Lyme disease between 2011–2020 after presenting to the emergency department, outpatient clinic, or inpatient admission at our tertiary care pediatric hospital and practice network in the Mid-Atlantic region. The initial electronic health record (EHR) query identified 1300 pediatric patients; 402 patients were likely eligible based on the following inclusion criteria: currently, 5–18 years old, confirmed prior diagnosis of Lyme disease, and absence of other chronic medical or psychiatric conditions prior to Lyme disease diagnosis. Potentially eligible participants were contacted by letter, followed by phone, email, and/or text message. Of these 402, 166 were reached and eligible, and 102 parents and 46 adolescents completed informed consent (parents) and assent (adolescents, if applicable) procedures and enrolled in the study. Demographic and EHR data were available for the full sample ($n = 102$). Ninety-nine parents and 46 adolescents completed validated patient- and adolescent-report questionnaires (Fig. 1). This study was approved by the Institutional Review Board at Children's National Hospital (Protocol #00009762).

Measures

Electronic health record data. Available clinical data from all initial and follow-up Lyme-related visits were extracted from the EHR. Lyme disease was summarized by stage and manifestation of disease (e.g., early localized, early disseminated, late). Two infectious disease experts (RD; AM) reviewed information to evaluate appropriateness and adequacy of the antibiotic regimen received for the treatment of Lyme disease.

Demographic information. Parents reported on demographic characteristics, including child sex, race, ethnicity, insurance type, parent sex, and parent marital status.

Lyme disease-specific medical information. Parents completed a detailed Lyme disease-specific medical information form designed for use in this study. Parents reported on their child's Lyme disease treatment, duration of overall symptoms prior to diagnosis, duration of overall symptoms post-treatment, and presence and duration of specific symptoms associated with PTLD symptoms or syndrome, including: (1) musculoskeletal pain; (2) fatigue; (3) difficulty thinking clearly; (4) depression; (5) significant reduction or inability to participate in daily activities; and (6) other symptoms (free text).

Validated parent- and adolescent-report questionnaires

Health-related quality of life: Parents and participating adolescents completed the Child Health Questionnaire Parent-Report (CHQ-P50) and Adolescent-Report (CHQ-CF87).[29] The CHQ has been validated in children with and without chronic conditions and assesses overall health, physical functioning, and psychosocial functioning across domains relating to the

child and related parent/family impact. Most items query functioning in the past 4 weeks; the change in health item refers to health as compared to 1 year ago and the global health item queries general health.[30,31] Individual subscale scores (range: 0–100) were calculated for parent and adolescent CHQ domains, with higher scores indicating better functioning. Individual subscale scores were used to calculate Physical Summary and Psychosocial Summary *t*-scores for the parent-report CHQ, with a mean score of 50 (standard deviation = 10). Higher scores indicate better health-related quality of life, with lower scores indicating moderate (≤40) or severe impairment (≤30).

PROMIS Computerized Adaptive Testing (CAT): Parents and participating adolescents completed PROMIS CAT measures evaluating Mobility, Fatigue, and Pain Interference. PROMIS measures have excellent psychometric properties.[32–35] Parents completed parent-proxy measures and participating adolescents completed self-report measures, reporting on functioning in the past 7 days. T-scores were calculated and compared to clinical cut-offs; higher scores indicate more of the construct (e.g., more mobility, more fatigue, more pain interference). Clinical T-score cut-offs include: Mobility – moderate difficulty (≤40), severe difficulty (≤30); Fatigue – moderate (≥55), severe (≥65); Pain Interference – moderate (≥55), severe (≥65).

Cognitive impact: Parents completed the Sluggish Cognitive Tempo scale to report on their child's cognitive functioning, including how true each of the 14 items was for their child.[36,37] Mean item scores were calculated (range: 0–3), with higher scores indicating more sluggish cognitive tempo.

Data analyses

Descriptive statistics, including frequencies, measures of average (means) and measures of spread (interquartile range, standard deviations) were calculated for demographic and clinical characteristics, including parent-reported duration of overall symptoms prior to diagnosis and duration of overall symptoms post-treatment. Parent report on the Lyme disease-specific medical information form also was used to identify a subset of children who experienced persistent symptoms (>6 months) post-treatment of Lyme disease with and without an impact on functioning.

To compare groups to categorical variables, we used Chi-squared tests and report Fisher's exact *p*-values. To compare groups to continuous measures, we used the Kruskal-Wallis test to avoid distribution assumptions. Correlations among continuous measures (e.g., parent- and adolescent-report scores) were calculated using Pearson correlation coefficient.

Measure total calculated scores, based on the manuals associated with each instrument, were used for statistical analysis and separate analyses to compare parent and adolescent report (when applicable). For the parent-reported CHQ summary scores and parent- and adolescent-reported PROMIS measures, raw scores were transformed into T-scores (mean = 50; standard deviation = 10). Calculation of T scores allowed for identification of participants reporting reduced quality of life or clinically significant symptoms on the CHQ and PROMIS measures in areas of functioning identified in the IDSA definition for PTLD symptoms or syndrome.

RESULTS

Patient characteristics

Demographics. Pediatric participants were, on average, 8.7 years old at Lyme disease diagnosis and 10.7 years old at study enrollment. Questionnaires were completed a mean of 2.0 years after initial Lyme diagnosis (range = 0.5–5.4 years). Enrollment differed by race and age, with participants of color and older children less likely to enroll in the study ($ps < 0.05$; Table 1)

EHR-reported Lyme disease characteristics and treatment. Of the 102 participants, 20 (20%) presented with single erythema migrans and were classified as early localized disease, 38 (37%) were classified as early disseminated disease, and 44 (43%) presented with arthritis and were classified as late disease (Table 2). Of enrolled subjects, older children and males were more likely to present with late disease ($p < 0.05$).

Eighty-nine participants (87% of the total sample) had sufficient EHR documentation to determine adequacy of antibiotic treatment. Seventy-six out of 89 (85%) participants received appropriate treatment for Lyme disease[5] and 13/89 (15%) were classified as potentially inadequately treated, most often due to the prescriber's use of amoxicillin dosing interval of every 12 h instead of every 8 h, which is a dosing interval not currently recommended by the guidelines for treatment of Lyme disease.[5]

Table 1. Demographic and clinical information for enrolled and non-enrolled participants.

	Enrolled ($n = 102$) *n* (%) or M ± SD	Non-enrolled ($n = 300$) *n* (%) or M ± SD
Child sex		
Male (%)	61 (59.2%)	189 (63.0%)
Child age at questionnaire completion (years)	10.7 years ± 3.2	Not applicable
Child age at diagnosis of Lyme disease	8.7 years ± 3.1	9.7 years ± 3.8
Time since initial Lyme diagnosis (years)	2.0 years ± 1.34	Not applicable
Child race		
White	75 (73.5%)	135 (45.0%)
Black/African American	10 (9.7%)	61 (20.3%)
Child ethnicity		
Not Hispanic/Latinx	86 (84.3%)	231 (77.0%)
Child health insurance type		
Public	12 (11.7%)	Not available
Parent sex Female (%)	87 (85.3%)	Not applicable
Parent Marital Status		
Married (%)	86 (83.5%)	Not available

Lyme disease-specific medical information form. Nine-nine parents provided information on their perceptions of their child's treatment and course of Lyme disease; three participants had missing data. One third of the sample (33/102; 32%) sought care from additional providers in addition to the facility where Lyme was diagnosed. Eleven participants (11%) reported use of one or more adjunctive therapies in addition to standard treatment, including: herbal supplements ($n = 8$), vitamins ($n = 7$), hyperbaric chamber treatment ($n = 1$), colloidal silver ($n = 1$), chiropractic treatment ($n = 1$), acupuncture ($n = 1$), and dietary changes ($n = 1$). None of the participants who reported use of adjunctive therapies were inadequately treated with standard therapies.

The majority of participants (55/102; 54%) reported that their child experienced symptoms up to 1 month prior to their diagnosis of Lyme disease. Participants with late disease were more likely to report longer symptom duration prior to diagnosis ($p < 0.01$). For overall duration of symptoms after Lyme disease treatment, most parents reported that their child's symptoms of Lyme disease resolved completely following treatment, although the time to full resolution was variable (Table 3). Eight-seven percent (77/89) of fully recovered patients did so within 6-months after completing initial antibiotic treatment, with 31% recovering within the first month post-treatment, 30% recovering 1–3 months post-treatment, and 14% recovering 4–6 months post-treatment. Eighteen parents (18%) reported their child took longer than 6 months to recover, with 6 of these parents (6%) reporting that their child was not fully recovered at the time of questionnaire completion. Duration of symptoms until recovery did not significantly differ by stage of Lyme disease (Table 3).

Table 2. Stage of Lyme disease at diagnosis for enrolled and non-enrolled subjects.

	Female ($n = 41$)	Enrolled ($n = 102$)		Non-enrolled ($n = 300$)	
		Male ($n = 61$)	Age (Mean ± SD)	Female ($n = 111$)	Male ($n = 189$)
Localized (single erythema migrans)	11 (27%)	9 (15%)	7.7 ± 2.8 yrs	31 (28%)	44 (23%)
Early disseminated (total)	17 (41%)	21 (34%)	8.3 ± 2.9 yrs	36 (33%)	47 (25%)
Lyme neuroborreliosis	6 (14%)	9 (14%)		Not available	Not available
Meningitis	3	7			
Facial Palsy[a]	3	2			
Multiple erythema migrans[a]	6 (14%)	6 (10%)		Not available	Not available
Other[b]	6 (14%)	6 (10%)		Not available	Not available
Late (Lyme arthritis)	13 (32%)	31 (51%)	9.6 ± 3.3 yrs	44 (39%)	98 (52%)

[a]One female who experienced both facial palsy and multiple erythema migrans was included in both the Lyme neuroborreliosis and multiple erythema migrans subheadings.
[b]Other category includes patients that experienced other manifestations of early disseminated disease including febrile illness with seroconversion (11) and carditis (1).

Table 3. Duration of symptoms prior to diagnosis and until recovery by stage of Lyme disease as assessed by parent report.

	Total Sample ($n = 102$)	Localized ($n = 20$)	Early disseminated ($n = 38$)	Late ($n = 44$)
Duration of symptoms prior to diagnosis[a]				
Less than 1 week	21 (21%)	7 (35%)	4 (11%)	10 (23%)
1–4 weeks	34 (33%)	7 (35%)	18 (47%)	9 (20%)
More than 1 month	40 (39%)	3 (15%)	14 (37%)	23 (52%)
Do not recall	4 (4%)	1 (5%)	1 (3%)	2 (5%)
Missing	3 (3%)	2 (10%)	1 (3%)	0 (0%)
Duration of symptoms until recovery[b]				
Less than one month	32 (31%)	8 (40%)	12 (32%)	12 (27%)
1–3 months	31 (30%)	7 (35%)	14 (37%)	10 (23%)
4–6 months	14 (14%)	1 (5%)	5 (13%)	8 (18%)
7 months or more	12 (12%)	0	4 (10%)	8 (18%)
Not recovered	6 (6%)	1 (5%)	2 (5%)	3 (7%)
Do not recall	4 (4%)	1 (15%)	0 (0%)	3 (7%)
Missing	3 (3%)	2 (10%)	1 (3%)	0 (0%)

[a]Chi square comparing type of Lyme disease by duration of symptoms prior to diagnosis was significant, with patients with Late disease more likely to have longer duration of symptoms prior to diagnosis ($p < 0.01$).
[b]Chi square comparing type of Lyme disease by duration of symptoms until recovery (collapsed into 3 groups due to small sample size: <1 month; 1–6 months; 7 months or more and not recovered) is not significant ($p = 0.38$).

In addition to reporting overall duration of symptoms after Lyme treatment, participants reported on the presence and duration of specific symptoms associated with PTLD symptoms or syndrome accordingly to the amount of functional impact. Twenty-two parents (22%) reported that their child experienced at least one symptom persisting >6 months post-treatment, including: fatigue ($n = 13$), musculoskeletal pain ($n = 11$), cognitive symptoms ($n = 10$) and depression ($n = 5$). Additional parent-reported symptoms identified in free text responses included: nightmares, mood swings, low appetite, headaches, high fevers, anxiety, and stomach pain. Thirteen of the 22 children (59%) had no significant impact on functioning and were classified as PTLD symptoms. Nine of the 22 children (41% of those with persistent symptoms, 9% of the total sample) had a significant impact on functioning and were classified as PTLD syndrome. Compared to the rest of the sample, children with PTLD symptoms and children with PTLD syndrome did not differ by child sex, race or ethnicity, stage of Lyme disease, or days since diagnosis. Older children were more likely to meet criteria for PTLD syndrome than younger children ($p = 0.03$).

The majority of participants with PTLD symptoms (10/13; 77%) or syndrome (8/9; 89%) were classified as adequately treated. Four of 13 (31%) participants with PTLD symptoms and 2 of 9 (22%) with PTLD syndrome reported use of adjunctive therapies. In terms of overall symptom duration, the majority of participants with PTLD symptoms (11/13; 85%) and syndrome (8/9; 89%) reported overall recovery at the time of questionnaire completion. Two of the three participants (one with PTLD syndrome and one with symptoms) whose parents indicated they were not recovered were classified as inadequately treated based on receipt of twice daily amoxicillin dosing. Of note, there were three additional participants who reported their child was not recovered but did not fulfill criteria for PTLD. One had persistent arthritis in one knee that was not painful nor impacted functioning; one had incomplete recovery of movement after facial palsy; and one had another medical diagnosis. Recovery status was not associated with adequacy of treatment. Participants with PTLD symptoms or syndrome were as likely to be adequately treated as those without PTLD symptoms or syndrome ($ps > 0.05$); those who reported they were not fully recovered ($n = 6$) were also as likely to be adequately treated as the rest of the sample ($p > 0.05$).

Table 4. Mean scores on validated parent- and adolescent-report questionnaires.

Measure	Parent mean score (SD)	Adolescent mean score (SD)	Correlations (*r*; *p* value) for parent and adolescent scores
CHQ (parent $n = 99$; adolescent $n = 46$)			
Physical Summary	53.88 (5.35)	Parent only	
Psychosocial Summary	50.66 (8.43)	Parent only	
Behavior	76.39 (16.84)	80.24 (13.01)	0.55†
Bodily Pain/Discomfort	82.24 (17.99)	79.34 (18.19)	0.49**
Change in Health	3.54 (0.94)	3.95 (0.94)	0.41**
General Health Perceptions	72.43 (16.94)	74.91 (13.96)	0.62†
Mental Health	75.51 (13.73)	75.48 (16.33)	0.61†
Physical Functioning	97.73 (5.80)	97.18 (4.57)	0.50**
Role/Social Limitations – Emotional/ Behavioral	93.15 (16.47)	Parent only	
Role/Social Limitations–Behavioral	Adolescent only	94.32 (15.65)	
Role/Social Limitations–Emotional	Adolescent only	86.23 (24.69)	
Role/Social Limitations – Physical	96.97 (9.92)	93.92 (15.82)	0.40**
Self-esteem	81.47 (20.38)	83.66 (17.87)	0.37*
Global Behavior	78.03 (21.46)	83.11 (15.93)	0.50**
Global Health	87.53 (16.18)	85.43 (15.01)	0.63†
Family Activities	85.50 (15.99)	85.82 (17.21)	0.71†
Family Cohesion	74.64 (21.61)	76.30 (25.85)	0.78†
Parental Impact–Emotion	73.98 (20.56)	Parent only	
Parental Impact – Time	90.58 (14.23)	Parent only	
PROMIS (parent $n = 96$; adolescent $n = 45$)			
Mobility	53.68 (6.06)	56.01 (6.29)	0.42**
Fatigue	43.40 (8.82)	40.21 (10.28)	0.65†
Pain Interference	44.04 (8.07)	39.52 (7.82)	0.37*
Cognitive Impact (parent $n = 97$)			
Sluggish Cognitive Tempo	0.56 (0.51)	Parent only	

For the CHQ physical summary and psychosocial summary scores, the mean T-score is 50 ± 10. Lower summary scores suggest poorer health-related quality of life. CHQ individual subscale scores range from 0–100 except for Change in Health which ranges from 1–5, with higher scores indicating better functioning. For the PROMIS scores the mean T-score is 50 ± 10, with higher scores indicating more of the construct (e.g., more mobility, more fatigue, more pain interference). For the Sluggish Cognitive Tempo scale, mean item scores range from 0–3, with mean item score indicating greater sluggish cognitive tempo. *$p < 0.05$; **$p < 0.01$; †$p < 0.001$.

Validated parent- and adolescent-report questionnaires (CHQ, PROMIS, Sluggish Cognitive Tempo)

Ninety-nine parents and 46 adolescents completed validated questionnaires. Mean scores for these measures were in the normative range, and parent and adolescent scores were highly correlated (Table 4).

Using parent report scores, a subset of scores in the total sample exceeded clinical cut-offs for moderate or severe impairment, including CHQ Physical Summary, CHQ Psychosocial Summary, PROMIS Mobility, PROMIS Fatigue, and PROMIS Pain Interference (Table 5). As compared to children who did not exceed the clinical cut-off, children with moderate/severe impairment did not differ by child age, race, ethnicity, stage of Lyme disease at diagnosis, age at diagnosis, or days since diagnosis. Parents of female children were more likely report moderate or severe pain interference using the PROMIS parent-proxy questionnaire than parents of male children ($p = 0.04$).

To better understand functioning in participants with PTLD syndrome, responses on parent- and adolescent-reported questionnaires were compared between children with PTLD syndrome and the rest of the sample. Children with PTLD syndrome did not differ on CHQ, PROMIS, and Sluggish Cognitive Tempo scores, with the exception that the PTLD syndrome group was more likely to have lower parent-reported CHQ Physical Summary Score ($M = 48.37 \pm 9.25$) vs. $M = 54.43 \pm 4.52$; $p = 0.01$), as well as more likely to exceed the clinical cut-off on parent-proxy PROMIS Fatigue measure ($p < 0.05$) (Table 5 and Fig. 2). Six out of nine participants identified as meeting PTLD syndrome criteria also had adolescent-report data. CHQ and PROMIS scores for these six adolescents did not significantly differ from those reported by adolescents who did not meet criteria ($ps > 0.05$).

DISCUSSION

This study systematically evaluated the prevalence of persistent symptoms following Lyme disease treatment in pediatric patients and assessed health-related quality of life and functioning using validated measures. Parent- and adolescent-report measures were selected to align with the IDSA definition of PTLD syndrome,[7] including reduced quality of life, mobility, fatigue, pain interference, and sluggish cognitive tempo. Most participants reported full resolution of symptoms at the time of questionnaire completion. However, there was variability in symptoms resolution time. The vast majority (87%) of fully recovered patients did so within the initial 6-month period after completing antibiotic treatment, with approximately one third recovering within the first month post-treatment and an additional third recovering 1–3 months post-treatment. However, 13% of children who

Table 5. Percentage of youth with moderate to severe scores on validated parent-reported health-related quality of life measures.

Measure	Total Sample	No prolonged symptoms	PTLD symptoms	PTLD syndrome	*P* value
CHQ Physical Summary[a]	1 (1%) $n = 99$	0 (0%) $n = 77$	0 (0%) $n = 13$	1 (11%) $n = 9$	ns
CHQ Psychosocial Summary[a]	12 (12%) $n = 99$	7 (9%) $n = 77$	3 (23%) $n = 13$	2 (22%) $n = 9$	ns
PROMIS Mobility[b]	1 (1%) $n = 96$	1 (1%) $n = 75$	0 (0%) $n = 12$	0 (0%) $n = 9$	ns
PROMIS Fatigue[c]	9 (9%) $n = 95$	3 (4%) $n = 75$	3 (28%) $n = 11$	3 (33%) $n = 9$	0.003*
PROMIS Pain Interference[d]	13 (13%) $n = 95$	8 (11%) $n = 75$	3 (27%) $n = 11$	2 (22%) $n = 9$	ns

Statistically significant between youth with and without prolonged symptoms.
ns non-significant.
*$p < 0.01$.
Moderate to severe impairment as indicated by: [a]Children Health Questionnaire (CHQ) parent-report Physical and Psychosocial Summary scores ≤ 40;
[b]PROMIS Pediatric Mobility score ≤ 40;
[c]PROMIS Fatigue score ≥ 55;
[d]PROMIS Pain Interference score ≥ 55.

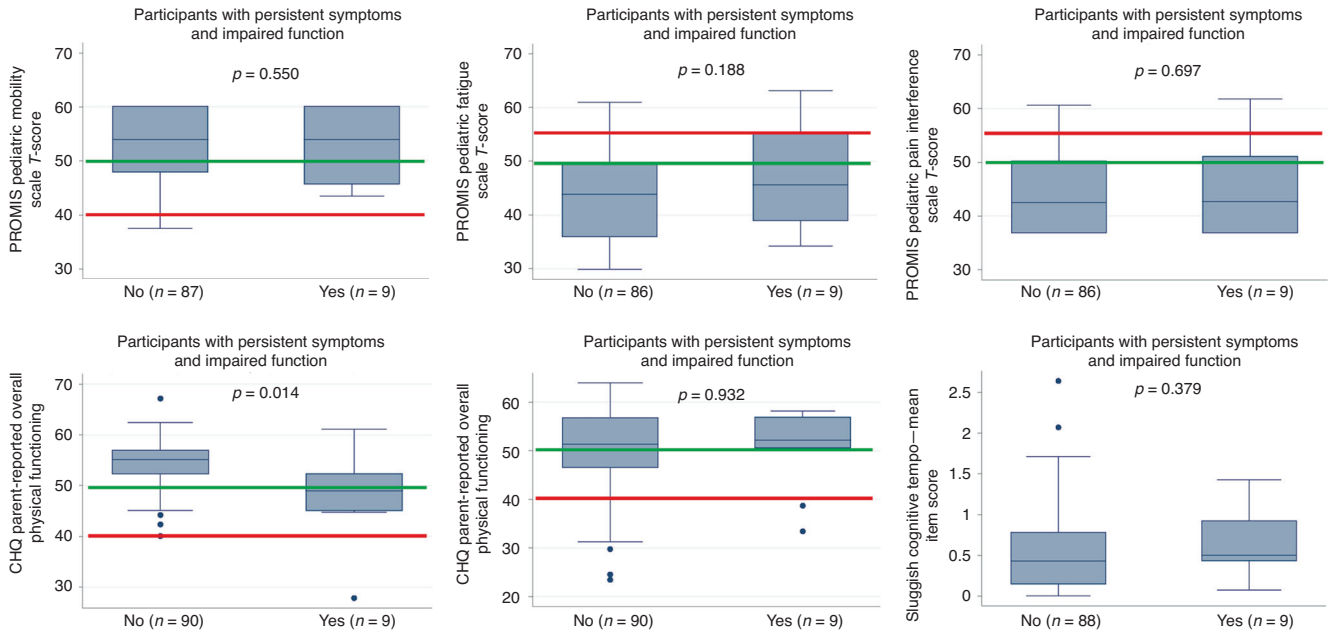

Fig. 2 Comparison of parent-report scores for participants meeting PTLD syndrome criteria (persistent symptoms and impaired function) and participants not meeting PTLD syndrome criteria.

ultimately made a full recovery took longer to do so. At the time of study completion, 6% of children still experienced symptoms attributed to Lyme disease and 1% experienced symptoms significant enough to impair daily functioning. It is important to reassure clinicians, patients, and families that recovery may be slower in some pediatric patients, but full recovery is achieved in most. Further, this information may discourage the use of potentially dangerous alternative therapies in children with a slower but ultimately successful trajectory of recovery.

A strength of the current study is the augmentation of EHR data with parent assessment of clinical course and recovery post-Lyme disease treatment. The majority of children received appropriate antibiotic treatment as documented in the EHR, consistent with current standards of care,[5] and adequacy of treatment did not differ among children with PTLD symptoms or syndrome and those without PTLD symptoms or syndrome. However, one-third of parents sought additional care for their child and 11% reported use of adjunctive therapies. Other studies relying solely on EHR data may be missing the full clinical course for patients who do not return to the initial treating clinician or pursue additional therapies.[20,24]

This study used parent- and adolescent-reported validated questionnaires to assess current functioning, allowing for comparison to normative samples.[6,38,39] We identified a small subset of children with moderate to severe impairment in health-related quality of life, mobility, fatigue, and pain interference. Reduced health-related quality of life related to psychosocial functioning and pain interference were most commonly reported. Impairment did not differ by stage of Lyme disease at diagnosis. Only physical functioning difficulties and fatigue were more common in children with PTLD syndrome, suggesting that some elevations may be attributed to causes other than Lyme disease.[38,40] It is reassuring that most questionnaire scores were in the normative range by the time parents and adolescents completed questionnaires, which was an average of 2 years after a diagnosis of pediatric Lyme disease. However, future studies incorporating prospective data collection starting at diagnosis of Lyme disease are needed to track the clinical course of symptoms in real time.

This study supports previous data that the overall prognosis for children to make a complete recovery from Lyme disease is excellent. Yet 9% percent of parents reported that their child may have met the adult case definition of PTLD syndrome, and an additional 13% experienced some persistent symptoms that did not significantly impact functioning (PTLD symptoms). These results are similar to other studies finding 85–97% of children

report resolution of symptoms 2–6 months post-Lyme disease.[20,24] Meeting criteria for PTLD syndrome was not associated with most demographic or clinical characteristics, including stage of Lyme disease or duration of symptoms prior to diagnosis. Older children were more likely to meet PTLD syndrome criteria. Further, as noted above, children with PTLD syndrome were rated by parents as having lower physical functioning and more fatigue, even though the majority reported recovery.

Limitations of the current study include a cross-sectional design, parental assessment of current functioning with variable time from initial Lyme disease treatment, and the lack of a matched comparison group. This study utilized electronic health records to identify pediatric patients with a history of Lyme disease; 41% of identified patients were able to be contacted and 61% of those reached and eligible enrolled in the study. It is possible that there was selection bias in those who agreed to participate, and pediatric patients with continued symptoms attributed to Lyme disease may be over-represented in the sample. Prospective data collected from the time of Lyme disease diagnosis and use of a comparison sample of children without Lyme disease could further inform and distinguish impairment attributed to Lyme disease from other causes that may impact functioning.[18] Other studies have found that some elevated symptoms are similar in patients with and without Lyme disease, suggesting that some prolonged symptoms may be inappropriately attributed to Lyme disease.[38,40] The current sample represents more diversity among patient-reported race and ethnicity than many studies with pediatric patients with Lyme disease. However, there were racial, ethnic, and age differences among those who enrolled in the study vs. did not enroll, which may limit generalizability of findings. It is important that future studies reflect the demographic diversity of the pediatric population diagnosed with Lyme disease.

The current study attempted to address limitations by excluding patients with pre-existing psychiatric or medical co-morbidities and using standardized tools to assess current functioning and severity of impairment. The selected parent- and adolescent-report questionnaires align with the PTLDS adult definition; however, few children met the strict adult criteria. Additional research is needed to support a pediatric-specific definition of PTLD syndrome. The current findings contribute to the operationalization of pediatric PTLD syndrome and the importance of multi-faceted assessment of the course and treatment of Lyme disease and related functioning. Future studies should prospectively evaluate initial Lyme presentation and the course of symptom resolution in pediatric Lyme disease to better understand common persistent symptoms and associations with patient and clinical characteristics. These studies should also assess patient and caregiver experiences.

Conclusions and future directions

These findings have important implications for clinicians treating pediatric patients with Lyme disease. Families should be counseled that full recovery is expected, and most patients recover in the first 6 months post-treatment, regardless of clinical presentation. Further, in the small percentage with prolonged symptoms with or without impact on functioning, full recovery will likely eventually be achieved. Effective communication with families about expected recovery rates and common symptoms that may persist after antibiotic treatment for Lyme disease can improve expectations and reduce the likelihood of seeking dangerous, expensive, and ineffective alternative therapies. For the small number of children who do not experience full recovery, more research is needed to better define the course and pathogenesis of their prolonged symptoms, as well as novel targeted therapies to relieve their suffering.

DATA AVAILABILITY

The data collected for the purposes of this study and analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

M.M. and R.D. made substantial contributions to the conception and design of the study, contributed to the analysis and interpretation of data, drafted the article, and revised it critically for important intellectual content. A.M. made substantial contributions to the conception and design of the study, contributed to the analysis and interpretation of data, drafted the article, and revised the article critically for important intellectual content. S.N. made substantial contributions to the acquisition of data and analysis of data, drafted the article, and critically reviewed the manuscript. M.G. and J.B. made substantial contributions to the analysis and interpretation of data and revised the article critically for important intellectual content. All authors provided final approval of the submitted manuscript.

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COMPETING INTERESTS

M.M. is currently employed by the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health. All data for this manuscript was collected prior to her employment at the National Institutes of Health. A.M. is employed by the National Institute of Allergy and Infectious Diseases, National Institutes of Health; A.M. has a patent (US 8,926,989) and serves as an unpaid scientific advisor to the Global Lyme Alliance and the American Lyme Disease Foundation. R.L.D., S.N., M.G., and J.B. declare no conflicts of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All participating parents and adult patients aged 18 years and up provided consent to participate in the study; adolescents ages 10 and up provided assent to participate in the study.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Roberta L. DeBiasi.