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Sleep quality in well-defined Lyme disease: a clinical cohort study in Maryland

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Abstract

Study Objectives

Lyme disease (LD) is the most common vector-borne disease in the United States. Approximately 5–15 per cent of patients develop postantibiotic treatment symptoms termed post-treatment Lyme disease syndrome (PTLDS). The primary objective of this study is to examine and quantify sleep quality among patients with early LD during the acute and convalescent periods, including among the subset who met criteria for PTLDS.

Methods

This paper draws from a clinical cohort study of participants with early LD ($n = 122$) and a subcohort of individuals who later met criteria for PTLDS ($n = 6$). Participants were followed for 1 year after antibiotic treatment. The Pittsburgh Sleep Quality Index and standardized measures of pain, fatigue, depressive symptoms, and functional impact were administered at all visits for participants and controls ($n = 26$). Participants meeting criteria for PTLDS at 1 year post-treatment were compared with a subset of PSQI-defined poor sleeping controls ($n = 10$).

Results

At the pretreatment visit, participants with early LD reported poorer sleep than controls. By 6 months post-treatment, participant sleep scores as a group returned to control levels. Participants with PTLDS reported significantly worse global sleep and sleep disturbance scores and worse fatigue, functional impact, and more cognitive-affective depressive symptoms compared with poor sleeping controls.

Conclusions

Participants with early LD experienced poor sleep quality, which is associated with typical LD symptoms of pain and fatigue. In the subset of patients who developed PTLDS, sleep quality remains affected for up to 1 year post-treatment and is commonly associated with pain. Sleep quality should be considered in the clinical picture for LD and PTLDS.

sleep and chronic pain, sleep quality, Lyme disease, post-treatment Lyme disease syndrome, Pittsburgh Sleep Quality Index

Statement of Significance

This is the first study to examine and quantify sleep quality in the context of well-defined early Lyme disease (LD) and post-treatment Lyme

disease syndrome (PTLDS). The findings provide support that sleep disturbance should be considered in the clinical picture of individuals with LD. Particularly for individuals who meet criteria for PTLDS, sleep quality may be poor and associated with the pain experience. Future research will need to validate these findings and expand upon them to evaluate and quantify sleep quality in individuals exposed to LD who are not well-defined and/or ideally treated.

Introduction

Lyme disease (LD), caused by the tick-borne spirochete *Borrelia burgdorferi*, is the most common vector-borne disease in the United States. The Centers for Disease Control and Prevention estimates that there are approximately 300000 new cases of LD each year in the United States, with the majority of these cases concentrated in the Northeast, Mid-Atlantic, and upper Midwest states [1]. Classic symptoms of early LD include a characteristic erythema migrans (EM) rash often accompanied by flu-like symptoms including fever, headache, and fatigue [2]. If left untreated, approximately 60 per cent of patients develop late stage LD which may manifest as intermittent bouts of arthritis or less commonly, chronic neurological issues [2]. Patients who are ideally diagnosed and treated usually recover completely with a 2 to 3 week course of doxycycline [3]. However, approximately 5–15 per cent of ideally treated patients develop what is termed post-treatment LD syndrome (PTLDS), characterized by persistent fatigue, musculoskeletal pain, and cognitive complaints that lead to functional decline [4]. The presence of one or more of these three symptoms beginning within the first 6 months after treatment for LD and continuing for at least 6 months is required to meet a proposed case definition for PTLDS [3].

To the best of our knowledge, no studies to date have examined and quantified sleep quality in the context of well-defined early LD or PTLDS; however, there is some anecdotal evidence which suggests that sleep problems may be a clinically notable feature of these conditions. Although the literature to date is limited, sleep problems characterized by difficulty falling asleep, difficulty staying asleep, and/or nonrestorative sleep have been noted in individuals with early LD [5]. In a review of the PTLDS literature, Marques notes that sleeplessness is one of the most common symptoms listed in studies of patients with PTLDS [6], despite not being an official part of the PTLDS–proposed case definition [3]. There has been one observational study of sleep quality in late LD. In that study, 11 patients with late LD were examined with polysomnography. The median length of uninterrupted stage two and stage four non-REM sleep was less in the patients with late LD than in healthy controls [7]. The authors concluded that the greater sleep fragmentation and irregularities in the sleep cycle found in those with late LD may contribute to the excessive difficulty initiating sleep, nocturnal awakenings, and daytime somnolence reported by patients with late LD [7]. Despite the findings of this study, sleep disruption has not yet been evaluated in the acute phase of early LD or longitudinally with specific standardized instruments used for measuring sleep quality.

The primary objective of the current study is to characterize the sleep quality of patients with well-defined, early LD at several time points across the acute and convalescent periods, including among the subset who met criteria for PTLDS. We sought to determine whether patterns in sleep quality identified over time among these patients differed from a sample of control participants and if relationships between sleep, pain, fatigue, and depressive symptoms existed. A 2009 poll by the National Sleep Foundation found that approximately 64 per cent of adults in the general population report some sleep problem at least a few nights a week. However, healthy adults tend to report better sleep, with 74 per cent indicating that their sleep needs are being met and 85 per cent indicating that they sleep 6 or more hours on a typical workday [8]. We hypothesize that participants with early LD (and in particular, participants with PTLDS) will report significantly worse sleep quality than control participants initially and that their sleep quality will improve over the course of the study after treatment.

Methods

The current study draws from a broader prospective study of LD conducted from 2008 to 2014 in a suburban community outside of Baltimore, Maryland. This study was approved by the Johns Hopkins Medicine Institutional Review Board. Participants were referred from either an urgent care facility or a primary care office. Eligible participants with LD ($n = 122$) were antibiotic-naïve at the time of enrollment and were required to present with an acute LD EM rash diagnosed by one of the authors (J.A.). Exclusion criteria included a self-reported history of prior LD, having received the Lyme vaccine, having Lyme symptoms for greater than 3 months duration, autoimmune disorders, chronic neurological disease, liver disease or hepatitis, HIV, cancer or malignancy in the prior 2 years, dementia, endorsing at least one item on the CAGE alcohol screen, current pregnancy, sleep apnea or narcolepsy, clinical depression, bipolar disorder, chronic fatigue syndrome (CFS), fibromyalgia (FM), and other chronic pain disorders. Controls ($n = 26$) were enrolled from the same referral network, matched to at least one case based on sex, age, and comorbidity (history of thyroid disease, heart disease, migraine headaches, and menopausal status, for women), and screened using the same exclusion criteria as cases. Informed consent was obtained from all case participants and controls prior to enrollment. Demographically, 52.5 per cent of participants with LD

were male compared with 46.2 per cent of controls; the mean age of participants with LD was 49.9 compared with 54.7 for controls; and participants with LD had 16.4 years of education on average, whereas controls had 17.8 (only years of education was significantly different between participants and controls).

All case participants were followed longitudinally for a total of four study visits: the time of initial clinical encounter (v1), 3 weeks post-treatment (v2, immediately after doxycycline treatment was completed), 6 months post-treatment (v3), and 1 year post-treatment (v4). Out of the 122 individuals who enrolled in the study and completed v1, one was lost to follow-up at v2 and eight were lost to follow-up at v3. Two participants missed v2, four participants missed v3, and two participants missed v4. Systematic data on reasons that participants were lost to follow-up were not taken because the majority of participants lost to follow-up were not able to be reached. No controls were lost to follow-up or missed any study visits.

At the time of initial clinical encounter (pretreatment), self-reported new-onset symptoms were elicited through a structured clinical interview to identify symptoms specific to their acute illness. All symptoms reported were followed up on through the duration of the study to see if they resolved, remained, or worsened over time. Additionally, at each of the follow-up visits, participants were given a separate 36-item, self-administered questionnaire developed by the authors to assess the severity of symptoms commonly reported by patients with PTLDS, including pain, fatigue, cognitive complaints, and sleep disturbances among others. Interviewers were consistent in the administration of both the clinical interview and questionnaire and did not probe for specific symptoms. At 1 year post-treatment, LD case participants were eligible to meet criteria for our proposed definition for PTLDS [9]. Although the IDSA–proposed case definition requires a minimum of 6 months of post-treatment symptoms [3], PTLDS status for the current study was assessed at 1 year post-treatment to identify participants with chronic symptoms of a longer duration. Briefly, PTLDS criteria were met if participants reported moderate or severe fatigue, musculoskeletal pain, or cognitive difficulties, as well as a composite T-score less than 45 on the 36-item Short Form Health Survey (SF-36) [10], indicating the impact of symptoms on daily life functioning since their last visit [9]. All other participants in the LD cohort who did not meet the proposed case definition for PTLDS at 1 year post-treatment are referred to as "non-PTLDS participants" in the current study. After obtaining informed consent, controls were seen at the four aforementioned time points over a 1 year period. Symptom measurements for controls were averaged across all visits at the individual level to yield one overall score for each control participant and to account for normal variability.

All study visits (for cases and controls) also incorporated self-administered surveys which included the Pittsburgh Sleep Quality Index (PSQI) [11], Fatigue Severity Scale (FSS) [12], Short Form of the McGill Pain Questionnaire (SF-MPQ) [13], Beck Depression Inventory-2 (BDI-II) [14], and SF-36 [10]. Cronbach's alpha, means, and standard deviations for these surveys are displayed in Table 1.

Table 1.

Participant and control performance on measures across all visits

	Cronbach's alpha	Participants with LD M (*SD*)	Controls M (*SD*)
PSQI	.767	4.65 (3.09)	4.12 (2.38)
FSS	.934	23.15 (13.46)	20.78 (9.23)
SF-MPQ	.915	3.07 (5.58)	1.31 (2.01)
SF-36	.938	52.31 (6.93)	55.09 (4.45)
BDI-II	.893	4.05 (5.12)	2.48 (2.85)

PSQI = Pittsburgh Sleep Quality Index; FSS = Fatigue Severity Scale; SF-MPQ = Short Form, McGill Pain Questionnaire; SF-36 = Short Form Health Survey; BDI-II = Beck Depression Inventory-II

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The PSQI measures sleep quality over the previous month using 19 self-rated questions that are grouped and scored into seven sleep components: subjective sleep quality, sleep latency, sleep duration, sleep efficacy, sleep disturbances, sleep medications, and daytime dysfunction. Each component is scored between zero and three inclusive, with higher scores indicating more severe difficulties within that sleep component. The sum of the seven-component scores yields the global sleep score which classifies respondents as either clinically "good" or "poor" sleepers; good sleepers have global scores of five or less, whereas poor sleepers have scores greater than five [11]. The diagnostic sensitivity and specificity of the PSQI are 89.6 and 86.5 per cent, respectively [11], and the instrument has been shown to have high construct validity [15].

The FSS measures the impact of fatigue and includes nine items that yield a total score between 9 and 63 inclusive, with greater scores indicating a greater impact (with a clinical cutoff of 36 indicating significant fatigue). The SF-MPQ captures total present pain with scores ranging from 0 to 45 inclusive, with higher scores indicating more pain; a cut-off score of 3 was chosen to indicate "high pain symptoms" which other studies found for healthy controls using this instrument [16, 17].

The BDI-II captures depressive symptoms and yields a total score between 0 and 63 inclusive, with higher scores indicating greater depressive symptoms (with a clinical cutoff of 14 indicates at least mild depressive symptoms indicating need for clinical attention). A two-factor structure of the BDI-II was used to differentiate between cognitive-affective and somatic depressive symptoms given that there can be an artificial inflation of the score as a result of the overlap of somatic symptoms of depression and physical symptoms of illness [18]. We sought to determine whether (1) participants (as a group) were above clinical cutoff on this instrument, indicating that clinical depression is part of the clinical picture for LD and (2) the driving symptoms are more cognitive-affective or somatic underlying those elevated scores.

The SF-36 measures the impact of health-related problems in several domains of life functioning. The total raw scores are normalized to T scores, with lower standardized scores representing poorer life functioning.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics v22. GraphPad Prism 6 was used for graphing data. All data were examined for the presence of outliers and to determine whether data were normally distributed. To compare the LD case cohort to controls on demographic, symptom, and cognitive variables, *t*-tests were used for normally distributed continuous variables and nonparametric Mann–Whitney U-tests were used for non-normally distributed ordinal data. The level of significance used for all analyses was $p < .05$.

Results

Group differences: early Lyme cases versus controls

Table 2 displays PSQI global scores (on a scale from 0–21) and all seven component scores (on a scale of 0–3) with higher scores representing greater sleep dysfunction. Symptom measurement scores are on their respective scales for all cases and controls. At the pretreatment visit (v1), in the structured clinical interview, 41 per cent of participants with early LD reported new-onset difficulty sleeping that they associated with the LD illness process. At this visit, the entire early LD cohort had a clinically and statistically significant global sleep score of 5.60 compared with controls score of 4.12 ($U = 1011.0$, $df = 130$, $p = .035$). Participants with LD scored significantly higher than controls on the subjective sleep quality component (indicating poorer sleep quality; $U = 1196.5$, $df = 144$, $p = .045$) and daytime dysfunction sleep component ($U = 1061.0$, $df = 142$, $p = .009$). There was also a notable trend for LD participating endorsing more often than controls that they had trouble sleeping specifically due to pain on an individual question contained in the sleep disturbances component ($U = 1191.0$, $df = 140$, $p = .069$). The difference in scores on the sleep medications component, which taps into if sleep medication (over-the-counter and/or prescribed) was used to help with sleep, indicated that controls used slightly more sleep medications than participants with LD ($U = 1249.0$, $df = 143$, $p = .049$), although both groups indicated using sleep medications less than once per week on average. Pain ($U = 591.0$, $df = 139$, $p = .000$), fatigue ($U = 1139.5$, $df = 145$, $p = .028$), and functional impact of symptoms ($U = 665.0$, $df = 113$, $p = .001$) were all significantly higher at the pretreatment visit in cases compared with controls. There was not a significant difference in cognitive–affective depressive symptoms between participants with LD and controls, though there was a statistically significant difference in somatic depressive symptoms ($U = 916.5$, $df = 145$, $p = .001$). This somatic subscale includes items such as loss of energy, tiredness, and changes in appetite. The finding likely represents an overlap with acute infectious symptoms present in this sample at this early time point. Still, the overall depressive symptoms for participants with LD (total BDI score) were not at clinically significant levels.

Table 2.

Symptoms and functional impact by group over time

	Participants with LD				Controls
	Pre-treatment (*n* = 122) M (*SD*)	Immediate post-tx (*n* = 119) M (*SD*)	6 months post-tx (*n* = 109) M (*SD*)	1 year post-tx (*n* = 107) M (*SD*)	(*n* = 26) M (*SD*)
Global sleep score	5.60 (3.24)*	5.12 (2.89)	3.91 (3.08)	3.86 (2.76)	4.12 (2.38)
Subjective quality	1.03 (0.75)*	0.93 (0.71)	0.58 (0.68)	0.60 (0.69)	0.68 (0.50)
Latency	0.79 (0.77)	0.73 (0.73)	0.62 (0.72)	0.64 (0.72)	0.64 (0.61)
Duration	0.60 (0.76)	0.54 (0.75)	0.44 (0.59)	0.42 (0.64)	0.42 (0.54)
Efficacy	0.54 (0.92)	0.41 (0.70)	0.30 (0.69)	0.19 (0.42)	0.31 (0.58)
Disturbances	1.32 (0.61)	1.21 (0.49)	1.05 (0.46)	1.11 (0.52)	1.15 (0.44)
Sleep medications	0.42 (0.88)*	0.34 (0.83)**	0.47 (0.90)	0.30 (0.76)**	0.54 (0.87)
Daytime dysfunction	0.92 (0.87)**	0.94 (0.81)**	0.52 (0.60)	0.54 (0.65)	0.44 (0.52)
Pain	6.18 (6.65)**	2.65 (5.50)	1.63 (3.53)	1.59 (4.70)	1.31 (2.01)
Fatigue	29.21 (15.48)*	24.81 (13.26)	18.94 (10.74)	18.72 (10.46)	20.78 (9.23)
Depressive symptoms	5.24 (5.44)*	4.64 (4.43)*	2.90 (4.73)	3.22 (5.51)	2.48 (2.85)
Cognitive/affective	2.23 (3.35)	2.29 (3.19)	1.66 (3.37)	1.97 (3.89)	1.34 (1.77)
Somatic	3.02 (2.71)**	2.35 (2.05)**	1.24 (1.77)	1.25 (2.00)	1.14 (1.24)
Functional impact	51.13 (6.39)**	50.29 (7.34)**	53.52 (6.40)	54.30 (6.67)	55.09 (4.45)

*$p < .05$; **$p < .01$.

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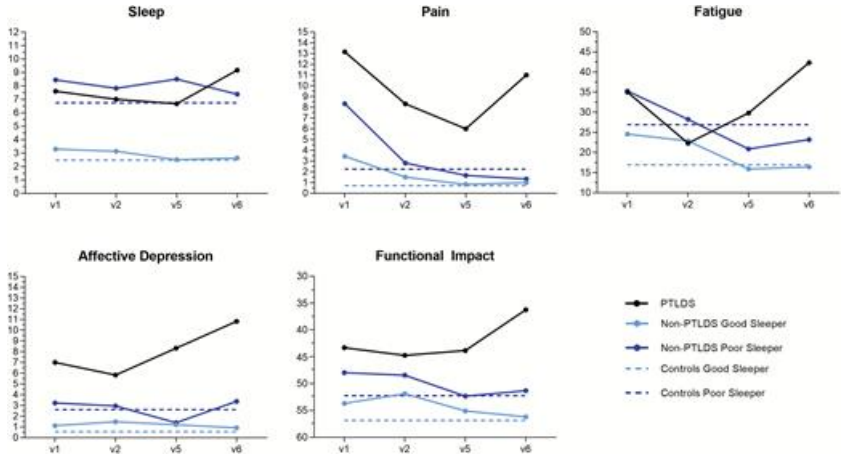
At the immediate post-treatment visit (v2), all sleep component scores improved slightly towards control levels except for the daytime dysfunction component, which increased/worsened marginally and remained significantly higher for participants with LD ($U = 995.5$, $df = 141$, $p = .004$). Pain and fatigue impact were no longer statistically significantly different from controls at v2, whereas functional impact remained significantly worse ($U = 870.0$, $df = 142$, $p = .001$). At 6 months post-treatment (v3), there were no significant differences between cases and controls on any sleep or symptom measure. At 1 year post-treatment (v4), the only significant difference between cases and controls was that cases had a lower sleep medications component score compared with controls.

Subgroup differences: PTLDS cases versus controls and non-PTLDS participants

Participants with LD who had persistent symptoms and met criteria for PTLDS at 1 year post-treatment ($n = 6$) were compared with controls who were found to be clinically poor sleepers according to the PSQI clinical cutoff score of five ($n = 10$). Poor sleeping controls were specifically chosen as the comparison group to determine whether PTLDS cases achieved quantitatively or qualitatively different sleep quality from those who are healthy and non-Lyme exposed, yet sleep poorly. PTLDS cases at 1 year post-treatment had a significantly greater global sleep score (indicating greater sleep problems) compared with the subset of controls who slept poorly (9.17 vs 6.74, $U = 10.0$, $df = 14$, $p = .03$). The sleep disturbances ($U = 10.0$, $df = 14$, $p = .03$) component was significantly worse in PTLDS cases, whereas the daytime dysfunction component approached significance ($U = 12.0$, $df = 14$, $p = .06$). Subanalysis of the sleep disturbances component found that four out of six PTLDS cases had moderate-to-severe trouble sleeping that they attributed specifically to pain, whereas only one out of ten poor sleeping controls indicated pain as the driving factor ($U = 3.0$, $df = 14$, $p = .002$). In addition, five of six PTLDS cases indicated having some trouble sleeping due to bad dreams, whereas only one of ten poor sleeping controls indicated this ($U = 10.5$, $df = 14$, $p = .03$). PTLDS cases also had significantly higher levels of fatigue (42.33 vs 26.91, $U = 10.0$, $df = 14$, $p = .03$), greater cognitive–affective depressive symptoms (10.83 vs 2.60, $U = 9.5$, $df = 14$, $p = .02$), and greater functional impact resulting from their symptoms (36.22 vs 52.25, $U = 0.0$, $df = 14$, $p < .001$). The finding for total pain in PTLDS cases was not statistically significantly different from controls (although it was trending towards significance), but the difference was clinically significant with PTLDS cases being above the clinical cutoff as a group (11.00 vs 2.25, $U = 14.5$, $df = 14$, $p = .09$). The lone component that poor sleeping controls scored worse on was the sleep latency component, though this result was neither statistically nor clinically significant.

Symptom scores for participants who met PTLDS criteria (PTLDS cases) at 1 year post-treatment are shown in Figure 1. At the 1 year time point when these participants with LD met PTLDS criteria, sleep, pain, impact of fatigue, functional impact, and cognitive–affective depressive symptoms were significantly worse for participants with PTLDS ($p \leq .001$ for each) than non-PTLDS participants. Looking retrospectively at the pretreatment visit for these PTLDS cases, pain, functional impact, and cognitive-affective depressive symptoms were significantly worse ($p = .037$, .009, and .004, respectively) compared with non-PTLDS participants at this visit. Figure 1 shows PTLDS participants', non-PTLDS participants', and controls' symptom measurements over the course of the study. Non-PTLDS participants and controls were further split into PSQI-criteria good and poor sleepers in the figure.

Figure 1.



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Symptom measurements over study duration across subgroups. Sleep (Pittsburg Sleep Quality Index), pain (Short-Form McGill Pain Questionnaire), fatigue (Fatigue Severity Scale), cognitive–affective depressive symptoms (Beck Depression Inventory-2), and funtional impact (Short Form Health Survey).

Discussion

This was a preliminary study to characterize sleep and investigate its relationship with pain, fatigue, and depressive symptoms in a cohort of participants with early LD over time. As was hypothesized, participants with acute infection during early LD were found to report significantly poorer sleep than controls, with LD participants' mean global sleep score falling above the PSQI clinical cutoff of five and controls' mean score falling below it. Although not all participants with LD reported new-onset sleep difficulties, a large minority (41 per cent) did indicate that new-onset sleep difficulties were a notable problem for them during this acute phase of LD. However, the magnitude of the difference in global sleep score between participants with LD and controls was less than expected, presumably because sleep problems are widespread in the general US population [8]. More specifically, the daytime dysfunction sleep component taps into both general sleepiness while performing activities such as eating, driving, and

socializing as well as enthusiasm for getting things done. Replicating what is found in the literature on early LD [5], participants with early LD in the present study had significantly worse daytime dysfunction scores than controls, with a component score more than double that of controls at both v1 and v2. This dysfunction likely continued into the post-treatment visit because it captured the entire antibiotic treatment period during which patients were recovering from their illness.

Participants with LD also endorsed significantly worse subjective sleep scores than controls at v1, indicating that they were aware of their new-onset sleep difficulties as a part of the illness picture prior to beginning their antibiotic treatment. Although the daytime dysfunction and subjective sleep quality components were the main drivers behind the overall increase in the global sleep score, all sleep components (sans the sleep medication component) were higher or worse in participants with LD than in controls.

Although controls used more sleep medications than participants with LD at all but one visit (v3), both groups reported minimal (less than once per week) usage of sleep medications on average. This level of sleep medication use as endorsed by controls in this study (0.54) is similar to the level found in healthy older adults in a pair of studies by Beaudreau and Spira (0.5 and 0.6) [19, 20]. Additionally, PSQI component and global scores in patients with insomnia have been found to be markedly higher compared with the present study's control participants. One study reported an average sleep medication component score of 1.07 and a global sleep score of 8.93 in patients with primary insomnia; both of these scores are approximately double that of controls' scores in the present study [21]. Therefore, despite the higher usage of sleep medications in the control sample, it is likely the usage reflects that of a healthy adult, and not someone with a sleep disorder such as insomnia. Furthermore, because cases and controls were drawn from the same referral population, we did not a priori expect a difference in the distribution of sleep problems between the two groups; more comprehensive and stringent sleep-medication exclusion criteria across both samples would likely not have changed the overall findings.

Other acute infectious diseases with similar presentations to early LD are sometimes accompanied by the presence of sleep disturbance. In a 2009 publication, Imeri and Opp noted that sleep is disturbed in a number of infectious diseases or illnesses and proposed that altered sleep is a component of the acute-phase response to infection, which promotes recovery. The purpose of these sleep alterations may be to facilitate generation of fever, as sleep architecture must be altered for this to happen [22]. Thus, the current findings of sleep difficulties in the initial phase of early LD are not unexpected and align with the illness process of an infectious disease. Investigating participants' sleep difficulties in the convalescent phase postantibiotic treatment allowed us to determine whether sleep problems continued or resolved in this cohort. By 6 months post-treatment, the majority of participants with LD had resolved both sleep symptoms and other symptoms, indicating a return to premorbid health. These signs of "return to health" persisted into the 1 year post-treatment visit, with the exception of the sleep medication component, which notably returned to a score better than control levels.

It is known that a subset of patients with early LD will continue to have symptoms of fatigue, pain, and/or cognitive complaints that lead to daily life functional decline after completion of antibiotic treatment [3, 4]. In the current study, six individuals were in this subset and met criteria for PTLDS at 1 year post-treatment. This convenience sample of participants with PTLDS, although small, allowed us to preliminarily investigate whether they exhibited sleep disturbance(s) and how sleep quality might be associated with other symptoms of PTLDS. Participants who met PTLDS criteria at 1 year post-treatment were compared with the subset of control participants who were clinically defined poor sleepers to determine whether the two groups had differing patterns of poor sleep quality and/or differing potential drivers of this poor sleep quality. The significantly higher global PSQI score in participants with PTLDS suggests that their sleep problems are more severe than those found in the poor sleeping control participants. In participants with PTLDS, the sleep disturbances and daytime dysfunction components were the major drivers in the overall difference in global sleep score compared with the poor sleeping controls. Delving further into the sleep disturbances component, having pain as well as having bad dreams was common in participants with PTLDS, but not in poor sleeping controls. Because sleep problems are common in the general population [8], these differences, although based upon preliminary evidence, may provide some indication of how the specific sleep difficulties in PTLDS may distinguish it from the sleep difficulties more commonly found in the general population.

There is evidence of sleep disturbance in other chronic conditions similar in presentation to PTLDS, such as FM and CFS. FM chiefly involves widespread bodily pain as well as abnormal pain processing, sleep disturbances, and fatigue [23]. FM also causes several sleep-related difficulties including early morning awakenings and nonrestorative sleep [24, 25]. There is evidence to suggest a relationship existing between pain intensity and sleep quality in FM [26]; one theory suggests that sleep problems in FM may stem from dysregulated mechanisms in the central nervous system (CNS) affecting the physiological processes which regulate sleep [27]. Also similar to PTLDS, CFS is a disorder characterized by 6 or more months of profound fatigue which is not improved by bed rest and is not due to other medical conditions associated with fatigue [28]. Patients with CFS record fewer hours of total sleep, have worse sleep efficiency, and spend less time in REM sleep compared with controls, which may be due to an imbalance of cytokines within the sleep network [29]. CFS has also been found to be associated with difficulty falling and/or staying asleep, nonrestorative sleep, and daytime sleepiness [30]. The significantly higher PSQI scores found in our participants with PTLDS (9.17 ± 2.99) are similar to scores found in populations of FM (13.22 ± 4.25) [31] and CFS patients (10.17 ± 4.02) [32]. Although the literature is not conclusive on what causes sleep disruption in FM or CFS, the potential mechanisms (e.g. pain or sleep bidirectional relationship, CNS disruption, and cytokine

imbalance) may give insight into the cause(s) of poor sleep in patients with PTLDS.

Countless studies have looked at the relationship between sleep quality and perceived pain. Regardless of the cause, pain, sleep, and fatigue are often reported as co-occurring [33]. Authors of early studies found the relationship between sleep quality and pain to be reciprocal [34]. More recently, a new trend has emerged which suggests that sleep disturbances may actually predict pain to a greater degree than pain predicting sleep disturbances [34]. The significant differences in pain experienced between participants with PTLDS and poor sleeping controls (that participants with PTLDS report sleeping poorly due to pain, but poor sleeping controls do not) indicate potential mechanistic differences in poor sleep quality between participants with PTLDS and poor sleeping controls. If, as recent research suggests, specific sleep irregularities in participants with PTLDS may be affecting pain levels [34], then improving sleep quality may be an important target for positively affecting more classic PTLDS symptoms such as fatigue, pain, and cognitive dysfunction.

Looking retrospectively at the pretreatment visit, pain, functional impact, and cognitive–affective depressive symptoms were each statistically worse in the PTLDS cohort than in both non-PTLDS participants and poor sleeping controls (Figure 1). We hypothesize that the increased magnitude of pain (in addition to the severity and multitude of other symptoms) may have adversely affected both the degree of functional impact and cognitive–affective depressive symptoms these individuals experienced during early LD. Pain, cognitive–affective depressive symptoms, and functional impact measurements remain worse in participants with PTLDS compared with both poor sleeping non-PTLDS participants and poor sleeping controls throughout the duration of the study. Fatigue for participants with PTLDS, however, improves from pretreatment to 3 weeks post-treatment, but then worsens beyond the levels of both poor sleeping groups by 6 months post-treatment. Because participants met PTLDS criteria at 1 year post-treatment, the largest differences between symptom measurements were found there.

With regard to the depressive symptoms, two individuals who later met criteria for PTLDS (out of six) had clinically significant depressive symptoms at visit 1 of the study, suggesting that they were “clinically depressed” upon presentation for study participation. Although all participants denied any history of clinical depression, these two individuals may have had subclinical depressive symptoms or undiagnosed depression prior to their exposure to LD. Nonetheless, at the 1 year follow-up, these two individuals continued to meet symptom cut-off criteria for clinically significant symptoms of depression (mild level) as did an additional three other individuals with PTLDS, for a total of five of the six in this small cohort. The endorsement of depressive symptoms by individuals with PTLDS may represent the emotional distress they are experiencing secondary to the overall illness experience and does suggest that over 1 year of follow-up that these individuals develop clinical depression as a cohort. These findings provide very preliminary evidence that it is important to screen for depressive symptoms in individuals with LD who report persistent symptoms of any type over the first year after exposure.

There are some limitations which may have affected our findings in the present study. The PSQI may not accurately capture the full extent of sleep problems experienced during the acute phase of LD. At the pre-treatment visit (v1), participants with LD had symptoms present for an average of 8.4 days prior to joining the study, but because the PSQI retrospectively looks at sleep over a longer period (the previous 30 days), it may not effectively gauge the severity of sleep disturbances specifically related to early LD at the time of diagnosis. Similarly, at the immediate post-treatment visit (v2), patients who recovered more quickly with antibiotic treatment may not have accurately recalled or reported their sleep difficulties towards the beginning of their treatment. Despite this, the PSQI has been shown to be a useful tool for capturing relatively stable periods of sleep. However, transient episodes of poor sleep, such as those that occur in the acute phase of LD, may be better examined using objective measures of sleep quality such as polysomnography to determine the mechanisms and different types of sleep abnormalities that may occur during acute infection. Polysomnography may also prove informative with patients with PTLDS, where it could yield objective confirmation of the population’s subjective sleep complaints, or, prompt future research into these subjective complaints via links to depression [35], the patient illness experience [36], or other unknown factors.

Participants with LD and controls may have entered the study with undiagnosed sleep disorders, unrecognized depression, other mental health disorders, or other symptoms that were not elicited in the self-reported questionnaire and may have affected symptom measurements and symptom relationships in later visits. However, it is unlikely that this could completely explain the group differences found in this study. We also had no reason to believe that the prevalence of these disorders, if present, would be distributed differently between cases and controls, since both groups were recruited from the same referral population.

Only participants with LD who presented with a diagnosable EM rash were included in the study; subgroups of patients with other presentations, such as neurologic LD, are not represented. Patients with neurological LD might be hypothesized to be at greater risk of poor sleep due to CNS infection. Another limitation of the present study was the relatively small sample size of PTLDS cases and control participants. Although statistical significance was found with many tests, a larger sample size may have resulted in more representative and generalizable findings.

In conclusion, the current findings provide preliminary support that sleep quality should be considered a part of the clinical picture of early LD and a relevant part of the symptomatology of PTLDS, despite not being included as one of the defining symptoms of the syndrome. In our control

population, poor sleepers were characterized by an overall increase in all seven-sleep component scores compared with good sleepers, whereas we found that among participants with PTLDS, poor sleep scores were driven by sleep disturbances (specifically having pain and/or bad dreams) and daytime dysfunction. As expected, pain played a more prominent role in the sleep quality picture for participants with PTLDS than for our control group and warrants further attention. Furthermore, although our sample size is small and further studies are needed, the patterns that we found in our participants with PTLDS were more similar to other medically unexplained syndromes, such as FM and CFS, than to our control population. The relationship between sleep, pain, and fatigue is important and additional studies are needed to delineate the causal relationships between these symptoms among patients with LD and PTLDS and its potential for a therapeutic target in the management of PTLDS.

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Notes

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