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Correlates of Perceived Health-Related Quality of Life in Post-treatment Lyme Encephalopathy

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Background: *Marked functional impairment has been reported by patients with post-treatment Lyme disease syndrome (PTLDS).* **Objective:** *We sought to identify the clinical features that contribute most strongly to the impaired health status associated with PTLDS.* **Methods:** *Enrolled patients had a well-documented history of Lyme disease, prior treatment with at least 3 weeks with intravenous ceftriaxone, a positive IgG Western blot, and objective problems with memory. An index score to capture aggregate cognitive functioning, Short-Form 36 physical and mental component summary scores, and scores on other clinical and demographic measures were examined. Multiple linear regressions were performed to determine significant predictors of perceptions of impaired life functioning as delineated by the Short-Form 36.* **Results:** *Fatigue was the most important contributor to perceived impairments in overall physical functioning, and fatigue and depression significantly predicted perceived impairments in overall mental functioning.* **Conclusions:** *Because fatigue and depression contribute prominently to reports of impaired physical functioning and mental functioning among patients with PTLDS, clinicians should assess patients for these symptoms and consider targeting these symptoms in the selection of treatment interventions. Future controlled studies should examine the effectiveness of such agents for patients with PTLDS.*
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Lyme borreliosis, caused by the tick-borne pathogen *Borrelia burgdorferi*, is a multisystemic illness that can adversely affect the skin, joints, heart, eyes, and nervous system.[1] In most cases, when Lyme borreliosis is recognized early, treatment is successful with a short course of antibiotics. However, treatment is less effective when infection is not recognized early, with a subset of patients reporting persistent and marked symptoms.[2,3] Some of these patients with persistent symptoms would have objective evidence of disease, such as those with chronic Lyme arthritis[4] or those with post-treatment Lyme encephalopathy (PTLE).[5] Others who do not have objectively measurable somatic markers of disease are said to have post-treatment Lyme disease syndrome (PTLDS)[6]; these patients typically report chronic subjective pain, fatigue, and cognitive impairment despite having received standard courses of antibiotic therapy.[2,5]

The symptoms of PTLDS are not specific and have been observed in other illnesses such as chronic fatigue syndrome (CFS)[7] and fibromyalgia.[8] For example, moderate to severe fatigue is an essential component of CFS and is also often a key component of PTLDS. In all three disorders (PTLDS, CFS, fibromyalgia), the chronic symptoms of fatigue or pain can be quite debilitating, representing more than the normal aches and fatigue of daily life. Differences among these

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disorders however are worth noting. The pain in PTLDS may be more focused than that in fibromyalgia, centering on certain joints or in the extremities due to a neuropathy.[3] The cognitive deficits in PTLDS may be more prominent than those in fibromyalgia[9] and CFS,[10] most often affecting memory, verbal fluency, and psychomotor speed, but also in some reports involving working memory and fine motor control.[5,11–14] Finally, biologic differences may be found among these syndromes; for example, a recent study demonstrated that the cerebrospinal fluid (CSF) proteomic profile of patients with PTLE differs from the CSF profile of those with CFS with 692 unique proteins in PTLE and 738 unique proteins in CFS.[15]

Two principal views have emerged regarding the etiology of these persistent symptoms; one attributes symptoms to persistent infection,[16] whereas the other posits a delayed immunologic response to prior infection or remnants of infection.[17,18] Because the etiology of post-treatment symptoms is uncertain and most likely heterogeneous with some patients having active infection and others a postinfectious process, for this article we use the term "PTLDS" if objective cognitive impairment is not present (or unmeasured) and "PTLE" if objective cognitive impairment is present.

Research has shown that in addition to experiencing debilitating symptoms, patients with PTLDS often report subjectively impaired functioning in the mental and physical domains.[19,5,2,20] One study examined associations between clinical features that appear early in the illness and functional outcome in PTLDS patients, but did not examine the influence of prominent clinical variables that manifest after treatment.[21] Knowing the extent to which commonly reported symptoms, such as cognitive impairment, pain, fatigue, or psychopathology, contribute to functional impairment would enable more targeted therapies for patients with persistent symptoms, while further elucidating their specific nature and influence in PTLDS.

The current study focuses on patients with objective cognitive impairment that persists after treatment for well-defined Lyme disease. This sample of patients with PTLE was used to determine the clinical correlates of perceived health status as measured by the Short-Form 36 (SF-36). We explored the effects of 2 prominent physical symptoms (pain and fatigue), psychopathology (depression and anxiety), and a summary index of cognition. For these clinical variables, we chose commonly reported persistent symptoms that best captured the multisystemic nature of the illness.[22] Owing to the severity of symptoms of pain and fatigue among these patients,[5] we hypothesized that these symptoms would have a strong negative effect on perceptions of physical functional status. Given the impaired functioning typically associated with depression and anxiety and the limitations imposed by cognitive deficits in PTLE, we hypothesized that these variables would have a negative association with self-reported mental functioning.

METHODS

Patients

Thirty-seven patients with a history of Lyme disease and cognitive impairment ("encephalopathy") who had participated in a randomized placebo-controlled treatment trial of persistent Lyme encephalopathy[5] were included in this study. Results of the treatment study have been described previously.[5] Briefly, between 2000 and 2004, individuals between the age of 18-65 years with a history of Lyme disease were recruited. All enrolled patients had a well-documented diagnosis of Lyme disease based on the Center for Disease Control–defined clinical and serologic surveillance criteria, a positive IgG Western blot for Lyme disease at the time of entry, a history of persistent cognitive impairment despite at least 3 weeks of intravenous (IV) ceftriaxone therapy, and subjective and objective evidence for memory impairment. Subjective memory impairment was based on self-report, with all patients complaining of problems with memory. Objective impairment was determined based on impaired performance of at least 1 SD below age-, gender-, and education-adjusted norms on core subtests of the Wechsler Memory Scale III. This level of impairment can be considered moderate and was used to define probable Lyme encephalopathy before study entry. Patients were excluded if they had pre-existing medical, psychiatric, or neurologic conditions that could account for cognitive impairment or if they had an allergy to ceftriaxone. Within the context of the clinical trial, patients received 10 weeks of randomized IV treatment with either ceftriaxone or placebo. Refer Table 1 for descriptive statistics on subject characteristics. The research protocol was approved by the New York State Psychiatric

TABLE 1. Descriptive Statistics on 37 Patients with Post-treatment Lyme Encephalopathy

	Mean (±SD)
Age (years)	45.47 (12.9)
Gender (% male)	43.24
Education level	14.69 (2.5)
Fatigue score	5.30 (1.3)
Beck depression score	11.76 (8.0)
Zung anxiety score	47.87 (10.7)
McGill pain score	5.05 (3.3)
Cognitive index score	−0.41 (0.6)
SF-36 Physical Component Summary score	35.74 (8.4)
SF-36 Mental Component Summary score	41.09 (11.2)

Institute, and all patients signed informed consent before study participation.

Assessments

All self-report assessments and cognitive testing were collected before the initiation of treatment in the clinical trial. While the screening battery for enrollment employed the Wechsler Memory Scale to identify objective memory impairment, the cognitive tests for the treatment study used a neurocognitive battery that has been shown to be sensitive to change and that focused on 6 cognitive domains: motor function (tests: finger tapping, simple reaction time, and choice reaction time), psychomotor function (tests: Trail Making A and B, and digit symbol), attention (tests: continuous performance test and Stroop task), memory (Bushke Selective Reminding Test and Benton Visual Retention Test), working memory (A not B logical reasoning test and N-Back test), and verbal fluency (Controlled Oral Word Association Test and Category Fluency Test). Information on these tests can be found in several outside sources.[23,24] *Z*-scores were obtained for patients' performance on each of these tests using age-, gender-, and education-adjusted norms.[5] Domain-specific scores were then calculated by averaging the *z*-scores for the tests within each respective cognitive domain. Cognitive index scores were obtained by averaging the domain scores for each patient; these scores were used to capture neurocognitive functioning within the context of this study. For psychopathology, the Beck Depression Inventory II[25] and the Zung Anxiety Index[26] were used. For energy, the Fatigue Severity Scale[27] was used. For pain, the visual analog scale for current pain of the McGill Pain Questionnaire[28] was used. To capture baseline perceived health status and functioning, the 2 SF-36 summary indices were used: the Physical Component Summary (PCS) and the Mental Component Summary (MCS).[29,30] Refer to Table 1 for the descriptive statistics on these measures.

Data Analysis

Statistical analysis was conducted using the software SPSS version 20 (Statistical Package for Social Sciences Inc., Chicago, IL). To determine whether a significant relationship existed between demographic and clinical variables and functional status as determined by scores on the SF-36, stepwise multiple linear regression analyses were conducted. Each regression examined the relative contribution to the SF-36 of the key variables: neurocognitive functioning as summarized by the cognitive index, psychopathology (Beck Depression Score and Zung Anxiety Index Score), physical symptomology (McGill Pain Score and Fatigue Severity Score), age, and gender. The outcome-dependent variables were the 2 summary indices of the SF-36 subscales: Physical Component Summary score (PCS) and Mental Component Summary score (MCS).

RESULTS

The majority of patients in this study were middle-aged with some college education. Slightly more women than men. Their physical symptom self-report scales revealed moderate to severe levels of fatigue and pain. Psychopathology was evident but not prominent, with minimal to mild levels of depression and anxiety. Although these patients were recruited for memory impairment, their cognitive index score revealed only a mild level of global cognitive impairment. Functional impairment however was severe, worse in the physical realm than in the mental realm.

The stepwise regression revealed that only the Fatigue Severity Score was significantly associated with the Physical Component Summary score. Results from this regression can be found in Table 2, and a graphical representation can be found in Figure 1. It was also found that the Beck Depression Score and the Fatigue Severity Score were significantly associated with the Mental Component Summary score. Results from this regression can be found in Table 3, and a graphical representation can be found in Figure 2.

TABLE 2. Stepwise Regression Results for Primary Outcome Variables (PCS and MCS)

Model 1 (DV: PCS)	*B*	Standard error	*β*	*t*	*p* value
Constant	52.124	5.044		10.333	0.000
Fatigue severity score	−3.092	0.924	−0.492	−3.347	0.002

*R^2 of this model is 0.24(F (1, 35) = 11.20, $p < 0.05$).
†VIF = 1; Durbin-Watson Test Statistic = 2.14.

It was inferred from relatively low variance inflation factors (VIFs) that multicollinearity was not a significant issue.[31] In addition, the Durbin-Watson test statistics were consistently above one, indicating that autocorrelation of errors was not a problem.[32] These values can be found in Tables 2 and 3.

DISCUSSION

The current study sought to determine the correlates of perceptions of impaired life functioning, as quantified by SF-36 Physical and Mental Component Summary scores, in a sample of patients with post-treatment Lyme encephalopathy.[5] Results demonstrate that fatigue is the most important contributor to the physical component summary (PCS) scale, accounting for 24.2% of the variance, and that both symptoms of fatigue and depression were significant contributors to the mental component summary (MCS), accounting for 71.6% of the variance. However, no significant associations were found among cognitive functioning, symptoms of anxiety, or symptoms of pain, and perceptions of health status. While it is clear that the measures of fatigue and depression together account for most of the variance in the mental functioning score, it is also clear that most of the variance in physical functioning was not accounted for by the variables we entered into the regression equation. This may be because the selected clinical variables were not the right ones, or this may have occurred because the measures were not sensitive or inclusive enough with respect to the full range of symptomatology in PTLE or PTLDS. For example, pain was assessed using a visual analog scale. While the visual analog scale has been well validated in pain research, there are other more detailed self-report measures of pain as well as experimental assays of pain tolerance (e.g., pressure pain or thermal pain thresholds) that may have been preferable for inclusion.

These results underscore the prominence of fatigue as a disabling symptom among patients with PTLDS. Persistent physical exhaustion and overwhelming tiredness contribute to impaired physical

FIGURE 1. Stepwise regression results: Physical Component Summary Score (Dependent Variable; Regression score was scaled to reflect direction of component scales).

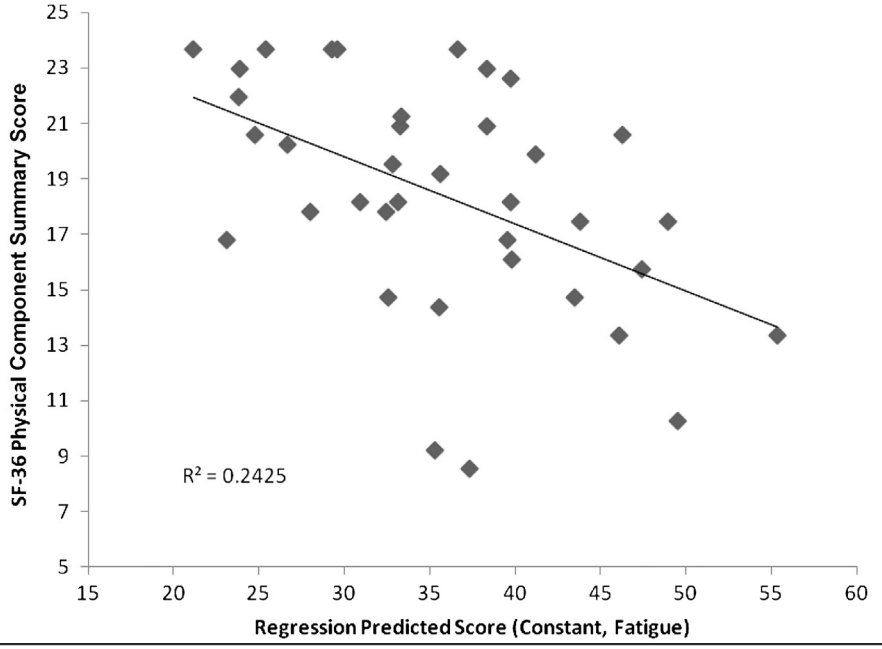


TABLE 3. Stepwise Regression Results for Primary Outcome Variables (PCS and MCS)

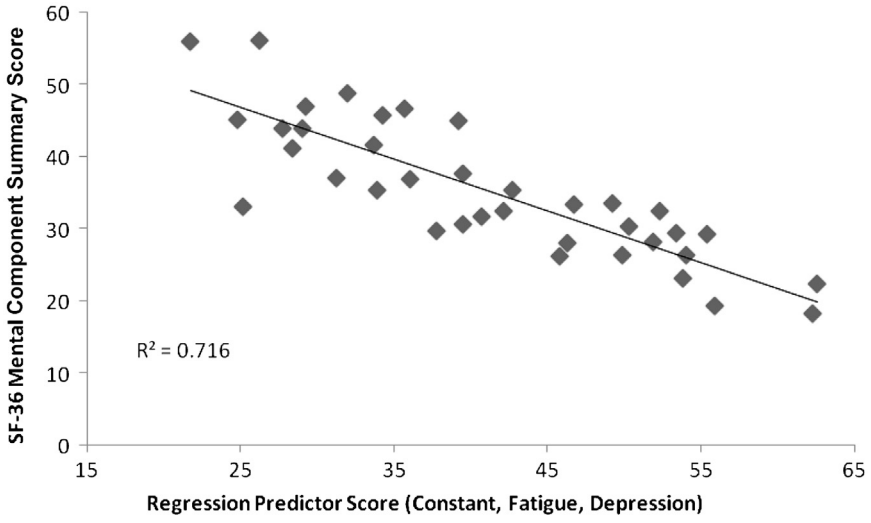
Model 2 (DV: MCS)	*B*	Standard error	*β*	*t*	*p* value
Constant	63.638	4.249		14.976	0.000
Beck depression score	−0.969	0.148	−0.692	−6.541	0.000
Fatigue severity score	−2.106	0.891	−0.250	−2.364	0.024

*R^2 of this model is 0.72 (F (2, 34) = 42.86, $p < 0.05$).
†VIF = 1.34; Durbin-Watson Test Statistic = 1.6.

and mental health. In addition to vitality, the Component Summary scales for mental functioning and physical functioning of the SF-36 include items that assess social functioning, one's ability to fulfill necessary roles due to affective and bodily issues, persistent psychologic distress, and one's inability to care for oneself.[33] The magnitude of fatigue in PTLDS is high—similar to that seen among patients with multiple sclerosis[27] and comparable to systematic lupus erythematosus.[34] However, the fatigue in PTLDS is not as circumstance dependent as that in multiple sclerosis.[34] Recent research indicates that patients with PTLDS may have an ongoing hyperactivated immune response with levels of antineuronal antibodies comparable to what has been reported among patients with systematic lupus erythematosus,[35] as well as elevated markers of interferon-α activity;[36] it is reasonable therefore to hypothesize that the fatigue among patients with PTLDS may be mediated partially by this immune-activated state.

The results of this study should lead clinicians to focus on treatment interventions designed to target persistent symptoms of fatigue. Current literature suggests that cognitive-behavioral strategies[37] and pharmacologic strategies[38] can be effective among some patients with persistently fatigued states. Whether additional antibiotic therapy among PTLDS patients with moderate to marked fatigue is indicated is an area of controversy in the medical literature. While the current guidelines of the Infectious Diseases Society of America[39] and the American Academy of Neurology[40] do not recommend repeated antibiotic therapy—partly due to the adverse risks associated with IV administration, these guidelines have been criticized for failing to encourage clinicians to discuss the actual study results with patients so that an informed risk-benefit decision could be made. A patient with marked to severe fatigue that impairs functioning may conclude that the possibility of a sustained reduction of fatigue as a result of repeated antibiotic therapy, as was demonstrated in one controlled study[41] and supported by a second controlled study,[5] may outweigh the risk of a serious adverse event from an indwelling catheter.[42,43]

FIGURE 2. Stepwise regression results: Mental Component Summary score (Dependent Variable; Regression score was scaled to reflect direction of component scales).



The observation that symptoms of depression were a major contributor to deteriorated perceptions of mental health status is of clinical importance. While a high prevalence of depression has been documented among patients with PTLDS,[22,44] the effect of depressive symptoms on perceived health and functioning in PTLDS has not been well studied. The items covering mental health functioning on the SF-36 that might be influenced by these symptoms include carelessness and reduced time in activities, accomplishing less than expected, and extent and time reduced in interpersonal events.[33] These study findings highlight the need to include appropriate psychopharmacologic and psychologic interventions for depression in treating symptoms of PTLDS. Clinicians should carefully assess depression among patients with PTLDS, perhaps with the assistance of self-report scales, such as the Beck Depression Inventory[25] or the Patient Health Questionnaire-9.[45] Although antibiotic treatment may result in an improvement in depressive symptoms among patients with active infection with *B. burgdorferi*, it should not be assumed that antibiotic treatment alone would be adequate to treat depression among patients with PTLDS. Research studies indicate that some patients who develop depression after acquiring Lyme disease may have depressive symptoms that persist despite having received considerable prior antibiotic treatment.[19,44] Because there are effective treatments for depression, patients with PTLDS may find that their lives are markedly improved as a result of such treatment, enabling them to cope with remaining somatic symptoms in a more effective way.

The clinical variables of interest in this study may interact. For example, fatigue can lead to poor motivation or effort on cognitive testing. Fatigue has also previously been correlated with memory impairment in patients with PTLDS,[12] although the current study did not find a significant correlation between fatigue and global cognitive impairment ($r = 0.10$). Depression may lead to decreased vitality, as was demonstrated by a significant correlation between depressive symptoms and fatigue ($r = 0.50$; $p < 0.01$). Depression may also lead to poor cognitive performance, but the correlation was not significant in our data set ($r = -0.01$). Finally, depression and pain are often related, as was shown by a significant correlation ($r = 0.46, p < 0.01$). The degree of variance however accounted for by these correlations is low, supporting their use as independent variables in the primary regression analysis. The relationship among depression, fatigue, and pain does suggest however that interventions targeting depressive symptoms in patients with PTLDS may, to some degree, also attenuate their fatigue and reduce pain.

Of note in this study is that the neurocognitive index summary score did not contribute significantly to the level of perceived mental or physical functional impairment. One possible explanation for this finding is that the cognitive deficits among these patients were only mild in severity. In addition, the sample size for this study was too small to be able to detect the contribution to impaired functioning of variables with lesser effect. Another possible explanation is that the SF-36 is not an adequate or sensitive measure of functional impairment in the cognitive realm. The SF-36 is a measure of health-related functional status that focuses in particular on physical and emotional health; as such, it may not have been constructed to detect the deficits in functioning seen among patients with mild to moderate cognitive impairment.

While the results of this report are compelling, they should be interpreted with caution. The patients enrolled in this study, while diagnosed using highly rigorous criteria for the definition of post-treatment Lyme encephalopathy, may be too narrowly defined to reflect the full population of patients with PTLDS. In addition, because the cohort for this report came from a prior treatment trial with explicit enrollment criteria, patients were excluded for many reasons, including negative serologic tests at screening, pre-existing psychiatric and neurologic conditions that might cause memory impairment, and current memory impairment that was not at least moderate in severity. These exclusionary criteria further limit the generalizability of our results to the larger community of patients with PTLDS. Finally, the sample size was small for the statistical analysis used in this study, and other variables that affect perceptions of health status may not have been recognized because their contributions to mental and health perceptions are more modest. Nonetheless, this is a rigorously defined sample of patients representing a disorder about which there is a great deal of controversy. Our goal was to identify those factors that had the largest and most significant effects on perceptions of health status, in order to assist clinicians who treat these patients.

In conclusion, the current study demonstrates that fatigue is the largest contributor to impaired

TABLE 4. Sample Questions from the SF-36[46]

1. Compared to 1 year ago, how much would you rate your health in general now?
2. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?
   a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports
   b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
   c. Lifting or carrying groceries
   d. Walking more than a mile
   e. Bathing or dressing yourself
3. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?
   a. Cut down the amount of time you spent on work or other activities
   b. Accomplished less than you would like
   c. Were limited in the kind of work or other activities
4. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
5. How TRUE or FALSE is each of the following statements for you?
   a. I seem to get sick a little easier than other people
   b. I am as healthy as anybody I know
   c. I expect my health to get worse
   d. My health is excellent

health-related functional status in both the physical realm and mental realm in patients with PTLDS and that depression plays a significant role in reducing perceived mental functioning. Future studies should be undertaken to test these findings in larger patient samples, with a particular focus on developing treatment strategies for these disabling symptoms (Table 4).

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