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ORIGINAL ARTICLE

Role of Psychiatric Comorbidity in Chronic Lyme Disease

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Objective. **To evaluate the prevalence and role of psychiatric comorbidity and other psychological factors in patients with chronic Lyme disease (CLD).**

Methods. **We assessed 159 patients drawn from a cohort of 240 patients evaluated at an academic Lyme disease referral center. Patients were screened for common axis I psychiatric disorders (e.g., depressive and anxiety disorders); structured clinical interviews confirmed diagnoses. Axis II personality disorders, functional status, and traits like negative and positive affect and pain catastrophizing were also evaluated. A physician blind to psychiatric assessment results performed a medical evaluation. Two groups of CLD patients (those with post–Lyme disease syndrome and those with medically unexplained symptoms attributed to Lyme disease but without *Borrelia burgdorferi* infection) were compared with 2 groups of patients without CLD (patients recovered from Lyme disease and those with an identifiable medical condition explaining symptoms attributed to Lyme disease).**

Results. **After adjusting for age and sex, axis I psychiatric disorders were more common in CLD patients than in comparison patients ($P = 0.02$, odds ratio 2.64, 95% confidence interval 1.30–5.35), but personality disorders were not. Patients with CLD had higher negative affect, lower positive affect, and a greater tendency to catastrophize pain ($P < 0.001$) than comparison patients. All psychological factors except personality disorders were related to level of functioning. A predictive model based on these psychological variables was confirmed. Fibromyalgia was diagnosed in 46.8% of CLD patients.**

Conclusion. **Psychiatric comorbidity and other psychological factors distinguished CLD patients from other patients commonly seen in Lyme disease referral centers, and were related to poor functional outcomes.**

INTRODUCTION

The term chronic Lyme disease (CLD) has been used to denote patients with chronic symptoms believed to be caused by persistent infection with *Borrelia burgdorferi*, often despite prior receipt of conventional 2–4-week courses of antibiotic therapy. Persistence of infection has never been substantiated in such patients (1,2), although there is some evidence from animal studies that viable *B burgdorferi* can persist despite antibiotic therapy (3). More importantly, many patients diagnosed as having CLD demonstrate no evidence, clinical or serologic, for prior *B burgdorferi* infection.

Eighteen years ago, one of the authors (LHS) reported that only 37% of patients evaluated at our academic Lyme disease referral center had current or previous infection with *B burgdorferi* as the explanation for their symptoms (4). A larger proportion of these patients met American College of Rheumatology (ACR) criteria for fibromyalgia (5) or had medically unexplained symptoms. Ensuing reports confirmed that a majority of patients presenting to Lyme disease referral centers had nonspecific symptoms, including musculoskeletal pain, fatigue, mood disturbances, and cognitive impairment that while largely idiopathic, were inappropriately attributed to CLD (6,7). Unfortunately, a diagnosis of CLD leads to multiple courses of antibiotic therapy and other interventions based on the flawed assumption of a persistent infection (4,8–13).

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Dr. Sigal gave legal review on Lyme disease care and possible vaccine-related adversities and received a fee.

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Patients with CLD are not homogeneous. Feder and colleagues described 4 categories of CLD patients seen in Lyme disease referral centers (14). Category 1 patients do not have objective laboratory evidence or clinical manifestations of infection with *B burgdorferi,* but are diagnosed as having CLD based on the presence of nonspecific symptoms, e.g., arthralgia, myalgia, fatigue, sleep disturbance, mood disturbance, and concentration problems. Category 2 patients also fail to have objective evidence of Lyme disease and instead have identifiable medical conditions or syndromes that explain the symptoms. Such patients typically adopt the diagnosis of CLD due to misdiagnosis or a patient's reluctance to accept a diagnosis like Parkinson's disease or multiple sclerosis. Category 3 patients have multiple nonspecific symptoms, no history of objective clinical findings for Lyme disease, and only equivocal evidence of antibodies for *B burgdorferi* on laboratory testing. Category 4, post–Lyme disease syndrome (PLDS), consists of patients with persistent nonspecific symptoms after infection with *B burgdorferi* and adequate antibiotic treatment. Across the categories, the distinguishing characteristics of CLD are a firm belief that CLD is at the root of one's symptoms and/or months or years of antibiotic treatment.

It is our clinical experience that the somatic manifestations displayed by many patients with CLD can be largely explained by the chronic distress associated with and exacerbated by several psychiatric disorders (11,12). Persistent psychological distress may result in physiologic manifestations such as autonomic nervous system dysfunction, neuroendocrine dysregulation, or sensitization of the central pain system. Other psychological processes such as harboring negative cognitions and certain emotional features may also play a role. Catastrophizing is a negative cognition characterized by pessimistic beliefs where the worst possible outcome is assumed, whereas poor affect is defined as observable emotion distinguished by high levels of negative affect (e.g., irritability, fear, hostility) and/or low levels of positive affect (e.g., strength, determination, enthusiasm). Poor medical outcomes in a number of chronic pain populations have been associated with catastrophizing (15,16) and poor affect (17,18).

Herein we evaluate the role that psychological factors may play in patients with CLD, as increased understanding would promote more effective treatment for the symptoms of these patients. We hypothesized that compared with patients with other medical conditions, CLD patients would have higher rates of psychiatric disorders, a greater tendency to catastrophize pain, higher levels of negative affect, lower levels of positive affect, and worse functional indices. A predictive model for group status based on these variables, CLD versus medical comparison groups, was tested.

PATIENTS AND METHODS

Patients and procedures. Participants were drawn from a cohort of 240 patients evaluated at the Lyme Disease Center at the University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School. All English-speaking patients ages 18–70 years seen at the Lyme Disease Center were invited to participate. Patients were enrolled and tracked from September 2002 through March 2007. Less than 17% of patients refused to participate or did not complete the study. Patients gave informed consent, completed questionnaires, and participated in structured clinical interviews when indicated by screening. Patients received $10 for study completion. The Institutional Review Board of the University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School approved this study.

Patients underwent standard medical evaluation for Lyme disease, including review of medical records (with special reference to prior laboratory testing), diagnostic interview, and physical examination. When Lyme disease was suspected and previous testing had not been conducted, 2-tier serologic testing (by enzyme-linked immunosorbent assay [ELISA] and Western blot) was used to assess the presence of antibodies for *B burgdorferi*. Patients diagnosed as having untreated Lyme disease were offered antibiotic therapy, reexamined at regular intervals, and called 6 months posttreatment for symptoms assessment. After the patient visit, the medical evaluator (LHS) blinded to questionnaire and interview findings logged observations and diagnosis. For all patients, non–Lyme disease explanations were explored and appropriate treatments and referrals were recommended. In cases where no diagnosis could be made, patients were tracked and reviewed (with LHS) upon receiving test or referral results.

Group definitions. To control for the effects of medical illness, our study design included 2 groups with CLD that were compared with 2 groups of medical patients without CLD. One CLD group had PLDS (Lyme disease immediately preceded chronic symptoms), whereas the other presented with medically unexplained symptoms thought to be CLD (MUSTB-CLD; Lyme disease did not immediately precede symptoms). Patients were identified for inclusion in this study based in part on the criteria for group membership below that were guided by the categories for CLD described by Feder et al (14). CLD patients were assigned to groups by investigators blinded to the results of the psychological assessment.

Post–Lyme disease syndrome. Patients must have at one time met Centers for Disease Control and Prevention (CDC) criteria for Lyme disease (19); however, PLDS patients no longer had clinical evidence of current infection upon evaluation (category 4 by Feder and colleagues) (14). These patients received adequate treatment, defined as meeting or exceeding guidelines from the Infectious Diseases Society of America (20). Patients attributed their symptoms to Lyme disease and reported no symptom-free period exceeding 6 months after initial infection.

Medically unexplained symptoms thought to be CLD. These patients fall into categories 1, 2, and 3 of CLD as described by Feder et al (14). No patients had objective clinical or unequivocal laboratory evidence of Lyme disease, but all attributed multiple physical symptoms to a current infection with *B burgdorferi*. To increase the homogeneity of the MUSTB-CLD group, all patients were

required to have received multiple courses of antibiotic treatment exceeding 90 days, which is a criterion not explicitly stated by Feder and colleagues (14). This timeframe far exceeds the recommended treatment duration of 14–28 days (13), and increases the likelihood that patients have had ≥3 courses of antibiotic treatment. The 90-day cutoff also eliminates patients given 1 course of antimicrobials prescribed as a precaution by their physicians; such patients typically were relieved not to have Lyme disease, and by no means held the conviction that Lyme disease was the only explanation for their symptoms. In contrast, a longer duration for antibiotic therapy is indicative of a population with greater conviction about the diagnosis. Extended treatment, even in the context of ongoing or unrelieved symptoms, is a marker for the degree to which these patients cling to the diagnosis of CLD.

Recovered from Lyme disease comparison group (LD comparison). Patients in the LD comparison group had a new onset of Lyme disease based on the CDC criteria (19) when initially presenting to the Lyme Disease Center. They were treated, followed for ≥180 days, and deemed to have recovered based on a standardized telephone interview assessing patient-reported presence of symptoms ascribed to Lyme disease 6 months posttreatment.

Medical diagnosis comparison group (DX comparison). This group consisted of patients whose current symptoms were explained by a medical condition (e.g., rheumatoid arthritis, multiple sclerosis) other than fibromyalgia or another similar syndrome. Most patients had been referred by physicians in the community to rule out a differential diagnosis of Lyme disease. Some of these patients had circumscribed antibiotic treatment. When antibiotic treatment exceeded 90 days, patients were classified as MUSTB-CLD based on the proposed category 2 of CLD by Feder et al (14).

Assessment measures. *Psychiatric comorbidity.* The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) classifies psychiatric disorders as either axis I (e.g., mood, anxiety, somatoform disorders) or axis II (personality disorders). Mood disorders are characterized by severe mood disturbances (i.e., depression, mania), whereas anxiety disorders include a number of related disorders whose key symptom is anxiety. In contrast, personality disorders are characterized by the presence of personality traits persistent, inflexible, and maladaptive enough to cause functional impairment and/or significant psychological distress (21). To assess axis I psychiatric disorders, patients were screened with the Patient Health Questionnaire for mood, anxiety, somatoform, eating, and substance use disorders (22). Positive screening results were verified using the corresponding module(s) of the Structured Clinical Interview for the DSM-IV (23). Personality disorders were assessed with the Millon Clinical Multiaxial Inventory-III (24), the most widely used written assessment instrument for evaluating personality disorders. The highest score for each patient determined personality style. To reduce false positives, a cutoff score of 90 was used instead of the customary 85.

Maladaptive pain coping, affect, and functioning measures. The catastrophizing subscale of the Coping Strategies Questionnaire (25) assessed catastrophizing, a trait characterized by pessimistic beliefs that the worst possible outcome will occur. This subscale has good construct validity (26) and is frequently used to assess the tendency to catastrophize pain in medical populations (15,16). The Positive and Negative Affect Scale was used to evaluate positive (e.g., enthusiastic, determined) and negative (e.g., upset, afraid) affect (27). Because fibromyalgia explains the symptoms of many CLD patients (4,7,28), a modified version of the Fibromyalgia Impact Questionnaire (FIQ) validated for patients with Lyme disease (29) determined the effect of symptoms on functioning (30,31). The FIQ has a mean of 50 and an SD of 10, with higher scores indicating worse functioning. The FIQ has good reliability and validity for the assessment of fibromyalgia-related physical functioning, well-being, and symptoms (30). Patients also completed a demographics form containing a checklist of 21 symptoms commonly reported by patients with CLD.

Statistical analyses. Data were analyzed (by SB) using generalized linear models, corresponding to linear regression for continuous variables (e.g., positive affect), logistic regression for categorical variables (e.g., group membership), or Poisson regression for number of symptoms. Age and sex were used as covariates throughout, but duration of illness was not, because it was a component of determination for group membership. Comparisons between groups were made using a contrast, giving equal weight to the 4 groups. Differences and odds ratios were adjusted for age and sex. *P* values for the 7 tests of group effects are given both unadjusted for multiplicity and with a Holm correction. Confidence intervals for effects are nominal. The predictive model was based on a hypothesized model, so model selection was not performed. Predictive power of the model was summarized with the Somers' Dxy rank correlation (32), which is based on the relative probabilities in discordant pairs; a value of 0.0 indicates random predictions, whereas 1.00 indicates perfect predictions. The R statistical environment was used for analysis (33).

RESULTS

Demographic and other subgroup characteristics. Seventy-seven patients were in the CLD group, 31 of whom were in the PLDS subgroup and 46 in the MUSTB-CLD subgroup. The CLD group was compared with 82 medical patients without CLD; 40 who had recovered from Lyme disease (LD comparison) and 42 with another medical condition that fully explained the presenting symptoms (DX comparison). Groups were similar demographically except for a higher proportion of women in the MUSTB-CLD and DX comparison groups; patients in the DX comparison group were somewhat older (Table 1). Because duration of illness was a determinant of group membership, longer duration was anticipated for the PLDS and MUSTB-CLD groups.

Based on 2-tier testing (ELISA and IgG immunoblot) as defined by the CDC (34), most (67.7%) patients with PLDS

Table 1. Demographics, reported symptoms, and antibiotic treatment history*

Characteristic	Nominal *P*	PLDS group (n = 31)	MUSTB-CLD group (n = 46)	LD comparison group (n = 40)	DX comparison group (n = 42)
Age, mean ± SD years	0.1748	42.4 ± 14.1	42.9 ± 12.3	43.4 ± 15.0	47.7 ± 12.3
Male sex	0.1761	14 (45.2)	8 (17.4)	20 (50.0)	13 (31.0)
White race	0.7447	29 (93.5)	37 (80.4)	36 (90.0)	38 (90.5)
Full-time employment	0.3248	12 (38.7)	23 (50.0)	17 (42.5)	26 (61.9)
College graduate	0.0196	13 (41.9)	19 (41.3)	22 (55.0)	28 (66.7)
Household income <$60,000	0.0852	14 (45.2)	22 (47.8)	14 (35.0)	13 (31.0)
Married	0.2117	22 (71.0)	26 (56.5)	31 (77.5)	29 (69.0)
Patient-reported					
Number of symptoms, mean ± SD	< 0.0001	8.7 ± 3.4	8.2 ± 3.0	6.5 ± 3.6	5.7 ± 3.1
Pain	0.9937	30 (96.8)	46 (100.0)	35 (87.5)	38 (90.5)
Fatigue	0.0208	29 (93.5)	40 (87.0)	32 (80.0)	28 (66.7)
Poor concentration	0.0050	24 (77.4)	31 (67.4)	23 (57.5)	18 (42.9)
Sleep disturbance	0.0010	24 (77.4)	30 (65.2)	20 (50.0)	17 (40.5)
Previous syndrome diagnosis†	0.0002	9 (29.0)	20 (43.5)	4 (10.0)	3 (7.1)
Tick bite	0.6143	6 (19.4)	7 (15.2)	12 (30.0)	6 (14.3)
Duration of illness, median months	< 0.0001	8	27	3	8
Documented or observed erythema migrans	0.7339	12 (38.7)	4 (8.7)	24 (60.0)	2 (4.8)
Positive ELISA	0.1718	21 (67.7)	10 (21.7)	26 (65.0)	4 (9.5)
Positive IgG immunoblot	0.2222	22 (71.0)	8 (17.4)	24 (60.0)	4 (9.5)
Physician-observed joint inflammation	0.0246	1 (3.2)	1 (2.2)	7 (17.5)	5 (11.9)
Physician-observed cranial nerve VII facial palsy	0.9999	5 (16.1)	—	6 (15.0)	—
Physician-diagnosed fibromyalgia	< 0.0001	8 (25.8)	28 (60.9)	1 (2.5)	2 (4.8)
Any antibiotic	0.9967	30 (96.8)	46 (100.0)	40 (100.0)	25 (59.5)
Oral antibiotic	0.1755	23 (74.2)	41 (89.1)	35 (87.5)	22 (52.4)
Multiple oral antibiotics	< 0.0001	10 (32.3)	33 (71.7)	11 (27.5)	5 (11.9)
IV/IM antibiotic	0.0002	13 (41.9)	24 (52.2)	12 (30.0)	3 (7.1)
Multiple IV/IM antibiotics	0.9903	2 (6.5)	12 (26.1)	1 (2.5)	—

* Values are the number (percentage) unless otherwise indicated. *P* values are omitted when empty cells caused unreliable model fits. PLDS = post–Lyme disease syndrome; MUSTB-CLD = medically unexplained symptoms thought to be chronic Lyme disease; LD comparison = recovered from Lyme disease comparison; DX comparison = medical diagnosis comparison; ELISA = enzyme-linked immunosorbent assay; IV = intravenous; IM = intramuscular.
† Fibromyalgia, irritable bowel syndrome, or chronic fatigue syndrome.

were currently positive for antibodies to *B burgdorferi*. In contrast, 18 (39.1%) MUSTB-CLD patients had a positive ELISA and a negative or equivocal finding on the IgG immunoblot analysis. Seven patients with MUSTB-CLD reported a prior tick bite and 4 had previous Lyme disease, with a recovery period >1 year before the onset of new symptoms was presumed to be another episode of Lyme disease. Six patients with medical diagnoses other than fibromyalgia were considered as having MUSTB-CLD, having received antibiotic treatment for >90 days. Their diagnoses included 1 case each of multiple sclerosis, Parkinson's disease, psoriatic arthritis, and osteoarthritis; 2 patients had neuropathy. ACR criteria for fibromyalgia (5) were met in 46.8% of CLD patients, or more specifically, in 60.9% of MUSTB-CLD patients and 25.8% of PLDS patients (Table 1).

Of the 40 LD comparison group patients, 24 were diagnosed based on the presence of erythema migrans: 8 had erythema migrans and positive serologic evidence (ELISA and IgG immunoblot), and 16 were diagnosed using serologic evidence and extracutaneous Lyme disease manifestations (e.g., 7 had Lyme arthritis, 6 had facial palsy). Of the 42 DX comparison group patients, 6 reported a recent tick bite, whereas 8 had a positive ELISA and/or a negative or equivocal finding on the IgG immunoblot analysis, and 2 reported a history of successfully treated Lyme disease (1 year and 14 years previously), but with new symptoms. Medical diseases and conditions found to explain symptoms are shown in Table 2.

Table 2. Medical diagnosis comparison group diagnoses

	Frequency (%)
Osteoarthritis	8 (19.0)
Rheumatoid arthritis	7 (16.7)
Multiple sclerosis	5 (11.9)
Neuropathy	5 (11.9)
Infection other than Lyme	4 (9.5)
Patellofemoral joint disease	4 (9.5)
Psoriatic arthritis	2 (4.8)
Sleep disorder	2 (4.8)
Encephalopathy	1 (2.4)
Impingement syndrome	1 (2.4)
Inflammatory joint disorder	1 (2.4)
Polymyalgia rheumatica	1 (2.4)
Undifferentiated connective tissue disorder	1 (2.4)

Table 3. Psychiatric comorbidity and other results*

	Nominal *P*	PLDS group (n = 31)	MUSTB-CLD group (n = 46)	LD comparison group (n = 40)	DX comparison group (n = 42)
Any axis I psychiatric disorder	0.0072	15 (48.4)	18 (39.1)	9 (22.5)	9 (21.4)
Current depression	0.0099	14 (45.2)	5 (10.9)	2 (5.0)	4 (9.5)
Past depression	0.8835	1 (3.2)	1 (2.2)	1 (2.5)	1 (2.4)
Dysthymia depression	0.1326	5 (16.1)	3 (6.5)	2 (5.0)	1 (2.4)
Any anxiety disorder	0.1364	9 (29.0)	9 (19.6)	6 (15.0)	5 (11.9)
Panic disorder	0.1459	4 (12.9)	5 (10.9)	3 (7.5)	1 (2.4)
Generalized anxiety disorder	0.3190	8 (25.8)	5 (10.9)	5 (12.5)	4 (9.5)
Posttraumatic stress disorder	—	—	1 (2.2)	—	—
Somatization disorder	—	2 (6.5)	4 (8.7)	—	1 (2.4)
Undifferentiated somatization disorder	—	1 (3.2)	4 (8.7)	—	—
Pain disorder	0.2199	3 (9.7)	5 (10.9)	3 (7.5)	1 (2.4)
Substance abuse disorder	—	1 (3.2)	—	1 (2.5)	—
Eating disorder	—	—	1 (2.2)	1 (2.5)	—
Any axis II personality disorder	0.2098	9 (29.0)	16 (34.8)	11 (27.5)	7 (16.7)
Histrionic	—	—	9 (19.6)	1 (2.5)	2 (4.8)
Narcissistic	0.3394	2 (6.5)	2 (4.3)	3 (7.5)	4 (9.5)
Compulsive	0.8138	1 (3.2)	4 (8.7)	5 (12.5)	1 (2.4)
Dependent	—	2 (6.5)	1 (2.2)	1 (2.5)	—
Schizoid	—	1 (3.2)	—	—	—
Other	0.9987	3 (9.7)	—	—	—
Functioning, mean ± SD	< 0.0001	55.9 ± 19.1	50.7 ± 18.8	38.5 ± 19.3	38.3 ± 18.2
Negative affect, mean ± SD	0.0263	25.0 ± 9.3	20.1 ± 7.0	19.8 ± 8.3	19.2 ± 6.4
Positive affect, mean ± SD	0.0003	28.6 ± 7.4	30.5 ± 9.0	33.0 ± 7.2	35.5 ± 6.6
Catastrophizing, mean ± SD	< 0.0001	13.1 ± 8.0	10.7 ± 7.5	5.8 ± 5.3	6.9 ± 7.7

* Values are the number (percentage) unless otherwise indicated. *P* values are omitted when empty cells caused unreliable model fits. See Table 1 for definitions.

Symptoms, misuse of serologic testing, and inappropriate antibiotic treatment. PLDS and MUSTB-CLD patients reported 37% more symptoms (95% confidence interval [95% CI] 22–55%) than the 2 comparison groups ($P < 0.001$, $P < 0.001$ with a Holm correction). Most PLDS patients reported pain (96.8%), fatigue (93.5%), poor concentration (77.4%), and sleep disturbance (77.4%). Similarly, all MUSTB-CLD patients reported pain and most reported fatigue (87%), poor concentration (67.4%), and sleep disturbance (65.2%). MUSTB-CLD patients presented with few observable clinical signs, e.g., joint inflammation, that could be misinterpreted as indicative of Lyme disease, although 4 MUSTB-CLD patients had documented a prior erythema migrans rash and successfully treated Lyme disease at least 12 months before the onset of new symptoms.

At baseline, pain and fatigue were common in the comparison groups (Table 1); however, poor concentration and sleep disturbance were less so. At followup, none of the LD comparison group patients reported pain or fatigue attributed to previous Lyme disease. Reports of tick bite, equivocal test results, and/or unreliable tests (e.g., Lyme urinary antigen test) or testing laboratories contributed to misdiagnosis in both MUSTB-CLD and DX comparison patients.

We deliberately used a rigorous cutoff (antibiotic treatment for >90 days) to enhance the specificity for inclusion in the MUSTB-CLD group. In addition to oral antibiotics, more than half of MUSTB-CLD patients received intravenous or intramuscular antibiotics (52.2%); 26.1% received multiple courses of intravenous or intramuscular treatment. Most patients in the DX comparison group received some antibiotic treatment (59.5%), including 5 (11.9%) who received multiple courses of oral antibiotics and 3 (7.1%) who received intravenous or intramuscular antibiotics, but the duration of treatment did not meet the >90-day criterion for MUSTB-CLD.

Psychiatric comorbidity. Approximately 20% of patients in both comparison groups met criteria for an axis I psychiatric disorder (Table 3). Rates of psychiatric disorders were significantly higher in PLDS and MUSTB-CLD patients compared with the comparison groups ($P = 0.007$, $P = 0.02$ with a Holm correction; odds ratio 2.64, 95% CI 1.30–5.35), with the highest rate observed in the PLDS group (48.4%). Current psychiatric disorders frequently found among patients with PLDS included major depressive disorder (45.2%) and generalized anxiety disorder (25.8%). Rates of personality disorders were elevated in the PLDS (29.0%), MUSTB-CLD (34.8%), and LD comparison (27.5%) groups. The difference between the comparison groups and the CLD groups was not significant (Table 3).

Associated cognitive, affective, and functional outcomes. MUSTB-CLD and PLDS patients were more likely than patients in the comparison groups to have higher levels of negative affect ($P = 0.02$, $P = 0.05$ with a Holm correction; difference 2.8, 95% CI 0.4–5.3), lower levels of

Table 4. Predictive model for group status in chronic Lyme disease*

Factor	OR (95% CI)	*P*
Age	0.90 (0.69–1.19)	0.48
Sex	0.78 (0.35–1.74)	0.54
Catastrophizing	2.21 (1.19–4.08)	0.0117
Negative affect	0.89 (0.49–1.62)	0.70
Positive affect	0.53 (0.31–0.91)	0.02
Axis I psychiatric disorders	1.20 (0.48–3.05)	0.69
Axis II personality disorders	2.19 (0.95–5.06)	0.07

* Odds ratios (ORs) for age, catastrophizing, negative affect, and positive affect are based on an increase of 10 units. Sex effect is for women. 95% CI = 95% confidence interval.

positive affect ($P < 0.001$, $P < 0.001$ with a Holm correction; difference 4.7, 95% CI 2.2–7.2), and a tendency to catastrophize pain ($P < 0.001$, $P < 0.001$ with a Holm correction; difference 5.2, 95% CI 2.9–7.4). MUSTB-CLD and PLDS patients showed worse functioning compared with comparison group patients ($P < 0.001$, $P < 0.001$ with a Holm correction; difference 14.5, 95% CI 8.5–20.5), scoring >1 SD below the scores earned by the comparison groups and the established mean on the FIQ. Poor functioning was related to catastrophizing ($r = 0.52$, $P < 0.001$), negative affect ($r = 0.49$, $P < 0.001$), and positive affect ($r = -0.40$, $P < 0.001$). Axis I psychiatric disorders were predictive of worse functioning for all patients ($P < 0.001$; difference 22.6, 95% CI 16.8–28.5).

Prediction model. The hypothesized prediction model consisting of age, sex, axis I psychiatric disorders, personality disorders, catastrophizing, positive affect, and negative affect accounted for group status ($P < 0.001$ compared with a base model of age and sex only) (Table 4), with a Somers' Dxy rank correlation of 0.49. Catastrophizing and positive affect significantly contributed to the model after accounting for other effects, with odds ratios for the joint PLDS and MUSTB-CLD groups of 2.21 and 0.53, respectively, for an increase of 10 on the catastrophizing scale or the positive affect scale.

DISCUSSION

Compared with 2 groups of medical patients, CLD patients had higher rates of axis I psychiatric disorders such as depression and anxiety, a greater tendency to catastrophize pain, higher levels of negative affect, lower levels of positive affect, greater number of symptoms, and worse functioning. Furthermore, lower levels of functioning were related to the presence of psychiatric disorders, higher levels of catastrophizing and negative affect, and lower levels of positive affect. These findings suggest that psychiatric comorbidity and other psychological variables play an important role in distinguishing CLD patients from other medical patients commonly seen in Lyme disease referral centers and in the functional outcomes of such patients. Patients in our medical comparison groups had axis I psychiatric disorders at rates similar to those estimated for the general population (21%) (35).

Rates of personality disorders did not vary significantly between groups; however, these rates were elevated in the PLDS (29.0%), MUSTB-CLD (34.8%), and the LD comparison groups (27.5%) in contrast to the DX comparison group (16.7%), which reflected rates closer to population norms (9–15%) (36,37). A prediction model for group status, taking into account age and sex and consisting of the presence of axis I psychiatric disorders and personality disorders, as well as level of catastrophizing, positive affect, and negative affect, was confirmed.

An observation that may have clinical utility is that distinct patterns of psychopathology were found for the different subgroups. For example, current depression was often observed in our CLD patients with PLDS (45.2%), but not in those with MUSTB-CLD (10.9%). This is consistent with other documented rates of depression in late Lyme disease that range from 26–66% (38), and the possibility that MUSTB-CLD patients may be more prone to somatization (i.e., expressing painful emotions through physical symptoms). The rate of current depression in our PLDS group is particularly striking, given that the general population estimate for mood disorder is ~7% (35). Also common in PLDS was generalized anxiety disorder, occurring in 25.8% of patients, which is notable because anxiety disorders have not been adequately studied in CLD even though panic attacks have been described during episodes of Lyme borreliosis (39). Lyme disease, at times affecting the central nervous system, has been associated with a number of psychiatric reactions (39); therefore, the elevated rates of psychiatric comorbidity in PLDS patients reported herein could be due in part to past infection with *B burgdorferi*. Although we did not formally assess sleep disorders, sleep disturbance was frequently reported by all groups, including the comparison groups. Sleep disturbance, pain, fatigue, and depression are characteristic of fibromyalgia (5), which was identified in >60% of our predominantly female MUSTB-CLD patients. Fibromyalgia has been previously observed in Lyme disease populations (4,7,28), and in some cases, it is thought that *B burgdorferi* may trigger fibromyalgia (40).

The results from this study should be interpreted cautiously. First, the cross-sectional design of our study makes it impossible to infer causality. Depression and anxiety could be the direct result of having Lyme disease, predisposing factors to CLD, a consequence of living with chronic physical symptoms, or a combination of all 3. To better evaluate the directionality of these relationships, we are conducting a longitudinal study that follows newly diagnosed and treated patients with Lyme disease over time. Second, some patients in our medical comparison group had the potential to become CLD patients. We used treatment with antibiotics for 90 days as a determinant of CLD status, but it was impossible to determine if some of the medical patients might continue to seek treatment in the future, thus eventually meeting our criteria for becoming MUSTB-CLD patients. Based on our clinical experience, the number of such patients should be relatively small, and if anything, may contribute to our underestimating the differences between those with CLD and those with medical illnesses and no CLD. Third, our patients may be unique in some other way, e.g., geography, in-

clined to seek treatment at Lyme disease referral centers; therefore, the rate of psychiatric comorbidity in our CLD group may not be representative of all CLD patients. Fourth, our ability to accurately assess the variables of interest, especially personality disorders, was limited by our instruments. Nonetheless, the behavior of our most challenging medical patients can frequently be explained by psychiatric comorbidity, especially personality disorders (41). Although we did not observe differences in rates of personality disorders between groups, it remains likely that a subgroup of patients with CLD likely accounts for much of the frustration reported by health care professionals providing treatment for CLD and other similar syndromes (42). Conversely, over half of our CLD patients had no psychiatric comorbidity; therefore, CLD cannot be described as a purely psychological condition. These patients are likely to be more psychologically resilient and may respond well to alternate explanations for their symptoms and more appropriate treatments targeting symptom reduction.

In summary, our data suggest an important role for psychiatric comorbidity in some patients with CLD. Axis I psychiatric disorders, but not personality disorders, distinguished CLD patients from other medical patients without CLD. Psychiatric disorders such as depression and anxiety disorders were highly prevalent in our PLDS group and were associated with a lower level of functioning in all groups. We also found that cognitive and affective variables, e.g., catastrophizing, negative affect, and positive affect, were related to level of functioning. The prominence of psychological factors in CLD suggests a place for a multidisciplinary treatment effort that centers on a cognitive–behavioral therapy type of approach, targeting mood, coping, and functioning. Such an approach has been shown to be effective for other populations with medically unexplained physical symptoms (43–45). Lastly, any therapy provided for these patients should not perpetuate the chronically sick role, but should instead promote symptomatic relief, wellness, and improved positive affect and quality of life.

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AUTHOR CONTRIBUTIONS

Dr. Hassett had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Hassett, Buyske, Gara, Escobar, Sigal.
Acquisition of data. Hassett, Radvanski, Sigal.
Analysis and interpretation of data. Hassett, Radvanski, Buyske, Savage, Gara, Escobar, Sigal.
Manuscript preparation. Hassett, Radvanski, Buyske, Savage, Gara, Escobar, Sigal.
Statistical analysis. Hassett, Buyske.
Literature review and logistics support. Savage.
Research mentor. Escobar, Sigal.

REFERENCES

1. Klempner MS. Controlled trials of antibiotic treatment in patients with post-treatment chronic Lyme disease. Vector Borne Zoonotic Dis 2002;2:255–63.
2. Marques AR, Stock F, Gill V. Evaluation of a new culture medium for *Borrelia burgdorferi.* J Clin Microbiol 2000;38: 4239–41.
3. Yrjanainen H, Hytonen J, Song XY, Oksi J, Hartiala K, Viljanen MK. Anti-tumor necrosis factor-α treatment activates *Borrelia burgdorferi* spirochetes 4 weeks after ceftriaxone treatment in C3H/He mice. J Infect Dis 2007;195:1489–96.
4. Sigal LH. Summary of the first 100 patients seen at a Lyme disease referral center. Am J Med 1990;88:577–81.
5. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33: 160–72.
6. Reid MC, Schoen RT, Evans J, Rosenberg JC, Horwitz RI. The consequences of overdiagnosis and overtreatment of Lyme disease: an observational study. Ann Intern Med 1998;128: 354–62.
7. Steere AC, Taylor E, McHugh GL, Logigian EL. The overdiagnosis of Lyme disease. JAMA 1993;269:1812–6.
8. Cameron D, Gaito A, Harris N, Bach G, Bellovin S, Bock K, et al, for the ILADS Working Group. Evidence-based guidelines for the management of Lyme disease. Expert Rev Anti Infect Ther 2004;2:S1–13.
9. Klempner MS, Hu LT, Evans J, Schmid CH, Johnson GM, Trevino RP, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. N Engl J Med 2001;345:85–92.
10. Sigal LH. The Lyme disease controversy: social and financial costs of misdiagnosis and mismanagement. Arch Intern Med 1996;156:1493–500.
11. Sigal LH, Hassett AL. Contributions of societal and geographical environments to "chronic Lyme disease": the psychopathogenesis and aporology of a new "medically unexplained symptoms" syndrome. Environ Health Perspect 2002;110 Suppl 4:607–11.
12. Sigal LH, Hassett AL. "What's in a name? That which we call a rose by any other name would smell as sweet." Int J Epidemiol 2005;34:1345–47.
13. Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2006;43: 1089–134.
14. Feder HM Jr, Johnson BJ, O'Connell S, Shapiro ED, Steere AC, Wormser GP, et al. A critical appraisal of "chronic Lyme disease" [published erratum appears in N Engl J Med 2008; 358:1084]. N Engl J Med 2007;357:1422–30.
15. Hassett AL, Cone JD, Patella SJ, Sigal LH. The role of catastrophizing in the pain and depression of women with fibromyalgia syndrome. Arthritis Rheum 2000;43:2493–500.
16. Edwards RR, Bingham CO 3rd, Bathon J, Haythornthwaite JA. Catastrophizing and pain in arthritis, fibromyalgia, and other rheumatic diseases [review]. Arthritis Rheum 2006;55:325–32.
17. Connelly M, Keefe FJ, Affleck G, Lumley MA, Anderson T, Waters S. Effects of day-to-day affect regulation on the pain experience of patients with rheumatoid arthritis. Pain 2007; 131:162–70.
18. Zautra A, Smith B, Affleck G, Tennen H. Examination of chronic pain and affect relationships: applications of a dynamic model of affect. J Consult Clin Psychol 2001;69:786–95.
19. Wharton M, Chorba TL, Vogt RL, Morse DL, Buehler JW. Case definitions for public health surveillance. MMWR Recomm Rep 1990;39:1–43.
20. Wormser GP, Nadelman RB, Dattwyler RJ, Dennis DT, Shapiro ED, Steere AC, et al, for The Infectious Diseases Society

of America. Practice guidelines for the treatment of Lyme disease. Clin Infect Dis 2000;31 Suppl 1:1–14.
21. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: text revision (DSM-IV-TR). 4th ed. Washington, DC: American Psychiatric Press; 2000.
22. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. JAMA 1999;282:1737–44.
23. First MB, Gibbon M, Spitzer RL, Williams JB. User's guide for the structured clinical interview for DSM-IV axis I disorders, research version (SCID-I, version 2.0, February 1996 final version). Washington, DC: American Psychiatric Press; 1996.
24. Millon T, Davis R, Millon C. MCMI-III manual. 2nd ed. Minneapolis: NCS; 1997.
25. Rosenstiel AK, Keefe FJ. The use of coping strategies in chronic lower back pain patients: relationship to patient characteristics and current adjustment. Pain 1983;17:33–44.
26. Swartzman LC, Gwadry FG, Shapiro AP, Teasell RW. The factor structure of the Coping Strategies Questionnaire. Pain 1994;57:311–6.
27. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988;54:1063–70.
28. Hsu VM, Patella SJ, Sigal LH. "Chronic Lyme disease" as the incorrect diagnosis in patients with fibromyalgia. Arthritis Rheum 1993;36:1493–500.
29. Fallon J, Bujak DI, Guardino S, Weinstein A. The Fibromyalgia Impact Questionnaire: a useful tool in evaluating patients with post–Lyme disease syndrome. Arthritis Care Res 1999; 12:42–7.
30. Burckhardt CS, Clark SR, Bennett RM. The Fibromyalgia Impact Questionnaire: development and validation. J Rheumatol 1991;18:728–33.
31. Bennett R. The Fibromyalgia Impact Questionnaire (FIQ): a review of its development, current version, operating characteristics and uses. Clin Exp Rheumatol 2005;23(5 Suppl 39): S154–62.
32. Somers RH. A new asymmetric measure of association for ordinal variables. Am Sociol Rev 1962;27:799–811.
33. R Development Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2007.
34. Centers for Disease Control. Recommendations for test performance and interpretation from the Second National Conference on Serologic Diagnosis of Lyme Disease. MMWR Morb Mortal Wkly Rep 1995;44:590–1.
35. US Department of Health and Human Services. Mental health: a report of the Surgeon General. Executive summary. Rockville (MD): US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Mental Health Services, National Institutes of Health, National Institute of Mental Health; 1999.
36. Grant BF, Hasin DS, Stinson FS, Dawson DA, Chou SP, Ruan WJ, et al. Prevalence correlates and disability of personality disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. J Clin Psychiatry 2004;65:948–58.
37. Lenzenweger MF, Lane MC, Loranger AW, Kessler RC. DSM-IV personality disorders in the National Comorbidity Survey Replication. Biol Psychiatry 2007;62:553–64.
38. Fallon BA, Nields JA. Lyme disease: a neuropsychiatric illness. Am J Psychiatry 1994;151:1571–83.
39. Fallon BA, Nields JA, Parsons B, Liebowitz MR, Klein DF. Psychiatric manifestations of Lyme borreliosis. J Clin Psychiatry 1993;54:263–8.
40. Steere AC. Musculoskeletal manifestations of Lyme disease [review]. Am J Med 1995;98:44S–51S.
41. Lamberg L. Personality disorder a possibility in "problem" patients, specialists say. JAMA 2006;296:1341–2.
42. Walker EA, Katon WJ, Keegan D, Gardner G, Sullivan M. Predictors of physician frustration in the care of patients with rheumatological complaints. Gen Hosp Psychiatry 1997;19: 315–23.
43. Carville SF, Arendt-Nielsen S, Bliddal H, Blotman F, Branco JC, Buskila D, et al. EULAR evidence based recommendations for the management of fibromyalgia syndrome. Ann Rheum Dis. 2008;67:536–41.
44. Woolfolk RL, Allen LA. Treating somatization: a cognitive-behavioral approach. New York: The Guilford Press; 2006.
45. Kroenke K. Efficacy of treatment for somatoform disorders: a review of randomized controlled trials. Psychosom Med 2007; 69:881–8.