CLINICAL RESEARCH STUDY

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Psychiatric Comorbidity and Other Psychological Factors in Patients with "Chronic Lyme Disease"

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ABSTRACT

BACKGROUND: There is no evidence of current or previous *Borrelia burgdorferi* infection in most patients evaluated at university-based Lyme disease referral centers. Instead, psychological factors likely exacerbate the persistent diffuse symptoms or "Chronic Multisymptom Illness" (CMI) incorrectly ascribed to an ongoing chronic infection with *B. burgdorferi*. The objective of this study was to assess the medical and psychiatric status of such patients and compare these findings to those from patients without CMI.

METHODS: There were 240 consecutive patients who underwent medical evaluation and were screened for clinical disorders (eg, depression and anxiety) with diagnoses confirmed by structured clinical interviews at an academic Lyme disease referral center in New Jersey. Personality disorders, catastrophizing, and negative and positive affect also were evaluated, and all factors were compared between groups and with functional outcomes.

RESULTS: Of our sample, 60.4% had symptoms that could not be explained by current Lyme disease or another medical condition other than CMI. After adjusting for age and sex, clinical disorders were more common in CMI than in the comparison group ($P < .001$, odds ratio 3.54, 95% confidence interval, 1.97-6.55), but personality disorders were not significantly more common. CMI patients had higher negative affect, lower positive affect, and a greater tendency to catastrophize pain ($P < .001$) than did the comparison group. Except for personality disorders, all psychological factors were related to worse functioning. Our explanatory model based on these factors was confirmed.

CONCLUSIONS: Psychiatric comorbidity and other psychological factors are prominent in the presentation and outcome of some patients who inaccurately ascribe longstanding symptoms to "chronic Lyme disease."

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KEYWORDS: Anxiety; Chronic Lyme disease; Chronic Multisymptom Illness; Depression; Fibromyalgia; Lyme disease; Psychiatric comorbidity

Lyme disease is a multisystem inflammatory disorder due to a symptomatic infection with the tick-borne organism *Borrelia burgdorferi*.[1] Clinical features, including erythema migrans rash, musculoskeletal pain, and joint in-

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flammation, typically resolve with conventional antibiotic treatment.[2] Rarely do patients treated with adequate antibiotic therapy continue to manifest objective evidence of ongoing infection. Yet, in studies of post-therapy complaints, 4%-40% of adult patients reported chronic physical, cognitive, or mood symptoms attributed to Lyme disease.[3-8]

Post Lyme Disease Syndrome refers to symptoms that continue 6 months after initial diagnosis and treatment.[2] Despite evidence from animal studies that viable *B. burgdorferi* can persist after antibiotic therapy,[9] there is no evidence of ongoing *B. burgdorferi* infection in humans.[10,11] Nonetheless, these patients are diagnosed as having "chronic Lyme disease"—assumed to be a persistent, perhaps incurable, infection.[12] Extended courses of antibiotic therapy are often prescribed for their "infection,"[2,13-16] even though double-blind, placebo-controlled studies have shown that such therapies provide no benefit.[17] Frequently, symptoms are best explained by fibromyalgia[4,14,16,18,19] and respond to treatment for this noninfectious disorder.

CLINICAL SIGNIFICANCE

- Misdiagnosis of Lyme disease was common, often resulting in repeated and unnecessary antibiotic treatment(s) for patients with well-defined medical conditions other than Lyme disease, as well as those with chronic diffuse symptoms or "Chronic Multisymptom Illness" (CMI).
- Psychiatric comorbidity, especially depression and anxiety, and other psychological factors distinguished CMI patients from those with medical conditions other than CMI.
- Psychiatric comorbidity and other psychological factors were associated with functional outcomes.

A second group of patients accounts for up to three quarters of patients seen in university-based Lyme disease referral centers.[14,19,20] These patients report multiple unexplained symptoms ascribed to "chronic Lyme disease" but do not have an illness or objective evidence explicitly suggesting Lyme disease. Some patients are self-diagnosed, while others are misdiagnosed by physicians using nonvalidated laboratory tests, applying alternative criteria in the interpretation of validated laboratory tests, or eschewing laboratory tests entirely, alleging fallibility and inaccuracy.[14,18,21] Many of these patients also inappropriately receive long-term or repeated antibiotic therapy.[2,14-16,19] Similar to Post Lyme Disease Syndrome patients, these patients experience numerous nonspecific complaints, for example, joint and muscle pain, fatigue, headache, and cognitive impairment, that are often complicated by depression,[16,19] psychological stress,[19] and the presence of other stress-related syndromes, especially fibromyalgia.[14,16,19,20] Conditions including, but not limited to, fibromyalgia, chronic fatigue syndrome, and Gulf War syndrome can be considered collectively as Chronic Multisymptom Illness.[22] The case definition for Chronic Multisymptom Illness has included having at least one or more chronic symptoms from at least 2 of 3 categories of symptoms including musculoskeletal, fatigue, and mood cognition.[22]

Previous findings and our own clinical observations suggest that the complaints of some patients presenting to Lyme disease referral centers might have explanations rooted in psychological distress.[16,19,23] Not only does mood disturbance appear to be common among these patients,[19] but one study found a relationship between prior psychological trauma or treatment with psychotropic medication and poor outcome in Lyme disease patients.[24] However, psychological factors have not been adequately studied in the full range of patients presenting to Lyme disease centers. Of importance are both broad categories of psychiatric conditions: clinical disorders (eg, depression, anxiety, somatization) and personality disorders (ie, inflexible, maladaptive, and enduring personality traits causing distress or functional impairment).[25] In addition to psychiatric disorders, maladaptive emotional and cognitive/coping factors associated with poor outcomes should be evaluated.

The objective of this cross-sectional study was to evaluate a large patient cohort representative of those seen in our Lyme disease referral center over the last 20 years. We assessed clinical and personality disorders, as well as a potential role for negative and positive affect (emotional state) and catastrophizing (maladaptive coping). Psychological factors were then compared between groups (those with and those without Chronic Multisymptom Illness) and with functional outcomes. An explanatory model for group inclusion consisting of clinical disorders, personality disorders, negative and positive affect, and catastrophizing was tested.

METHODS

Participants

We recruited 240 patients from the Lyme Disease Center at the University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School (UMDNJ-RWJMS). Participants were predominantly residents of New Jersey, New York, Connecticut, and Pennsylvania—areas endemic for Lyme disease. Most were referred by physicians in their communities, while others were self-referred. The Institutional Review Board of UMDNJ-RWJMS approved this study.

Procedures

All English-speaking patients aged 18-70 years presenting to the Lyme Disease Center for an initial visit were invited to participate. Enrollment and tracking took place from

September 2002 through March 2007. Patients arrived 1 hour before their appointment and completed consent forms and questionnaires in a private room. Structured clinical interviews were conducted when indicated by screening. Fewer than 17% (49 patients) declined to participate or did not complete at least 75% of the questionnaires. Participants were paid $10.

LHS conducted a standard medical evaluation for Lyme disease including a diagnostic interview, physical examination, and chart/records review. Special reference was given to the results and location of prior laboratory testing. Two-tiered serological testing (enzyme-linked immunosorbent assay and Western Blot) was ordered when current but previously undiagnosed Lyme disease was suspected. For patients diagnosed as having untreated Lyme disease, antibiotic therapy was offered. These patients were reexamined at regular intervals and contacted by telephone 6 months post-treatment to evaluate the persistence of Lyme disease-related symptoms. Explanations other than Lyme disease were sought for all patients' complaints, for example, osteoarthritis, systemic lupus erythematosus, fibromyalgia, Parkinson disease, amyotrophic lateral sclerosis, antiphospholipid antibody syndrome (all diagnoses made in the past in patients referred for evaluation of Lyme disease),[14] and appropriate treatments and referrals were recommended. When diagnosis was unclear, patients were tracked and reviewed by LHS upon receiving test or referral results. Blind to questionnaire findings, LHS assigned patients to 1 of 4 groups described below.

Chronic Multisymptom Illness Group 1: Post Lyme Disease Syndrome. These patients met Centers for Disease Control (CDC) criteria for Lyme disease[26] (Table 1); in most cases the 2-tiered protocol for laboratory tests provided seroconfirmation. They received adequate prior antibiotic treatment defined as meeting or exceeding guidelines from the Infectious Diseases Society of America,[27] but continued to report persistent symptoms ascribed to Lyme disease. At evaluation there was no evidence of inflammatory disease that could be ascribed to active *B. burgdorferi* infection and no serologic evidence of infection with *B. burgdorferi* that had not been treated previously with adequate antibiotic therapy.

Table 1 Centers for Disease Control (CDC) Criteria for Lyme Disease

Clinical case definition
Erythema migrans (≥5 cm in diameter) or
At least one late manifestation; these include: musculoskeletal, nervous, or cardiovascular system involvement. Base this assessment solely on objective clinical criteria of disease in that organ system, and laboratory confirmation of infection.
Laboratory criteria for diagnosis
Isolation of *Borrelia burgdorferi* from clinical specimen, or
Demonstration of diagnostic levels of IgM or IgG antibodies to the spirochete in serum or cerebrospinal fluid, using serological techniques based on *Borrelia*-specific antigens.
Significant change in IgM or IgG antibody response to *B. burgdorferi* in paired acute- and convalescent-phase serum samples.

IgM = immunoglobulin M; IgG = immunoglobulin G.

Chronic Multisymptom Illness Group 2: Fibromyalgia. These patients did not meet CDC criteria for Lyme disease at the onset of their symptoms;[26] nonetheless, symptoms were attributed to Lyme disease. These patients met the American College of Rheumatology criteria for fibromyalgia[28] and no other medical condition.

Chronic Multisymptom Illness Group 3: Medically Unexplained Symptoms. These patients did not meet CDC criteria for Lyme disease at the onset of their symptoms[26] and their multiple symptoms could not be accounted for by a medical condition. There was little or no evidence of fibromyalgia at evaluation.

Comparison Group. Patients without Chronic Multisymptom Illness included those diagnosed by LHS as having previously untreated Lyme disease based on CDC criteria.[26] These patients were offered antibiotic therapy and contacted 6 months post-treatment for a telephone interview. Patients denying symptoms related to Lyme disease were considered recovered and assigned to the comparison group. Others without Chronic Multisymptom Illness had well-defined medical conditions, for example, osteoarthritis, or were deemed "healthy," meaning that they had no chronic symptoms but were concerned about possible exposure, for example, found tick on clothing.

Assessment Measures

Most studies assessing psychiatric comorbidity typically consider "depression" or "anxiety" using questionnaires that rarely result in a concrete diagnosis. Herein, participants were evaluated rigorously for the presence of clinical disorders like Major Depressive Disorder, Generalized Anxiety Disorder, and Post-traumatic Stress Disorder. The PRIME MD Patient Health Questionnaire was used to screen patients for the presence of clinical disorders, which, for the purposes of this study, included diagnoses falling under the broader categories of mood, anxiety, somatoform, eating, and substance use disorders.[29] Next, to explore positive screening results, corresponding modules from the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*[30] were used to identify definitive diagnoses.

Psychiatric comorbidity also includes personality disorders; however, this other broad category is rarely explored. Personality disorders can co-occur with clinical disorders, but by definition represent an enduring pattern of maladaptive personality traits that are relatively stable over time and apparent in the absence of a clinical disorder such as Major

Depressive Disorder.[25] The most extensively used written assessment instrument for personality disorders, the Millon Clinical Multiaxial Inventory-III,[31,32] was used to evaluate personality disorders. The single highest scale score was considered the best indicator of personality style. A cutoff score of 90 was used instead of the traditional cutoff score of 85 to reduce false positives.[33]

The Coping Strategies Questionnaire's catastrophizing subscale[34] assessed catastrophizing, a dysfunctional cognitive process associated with poor medical outcomes in rheumatologic populations.[35] Catastrophizing is characterized by pessimistic beliefs where one anticipates the worst-case scenario. The catastrophizing subscale has good construct validity.[36] The Positive and Negative Affect Scale evaluated emotional characteristics.[37] This reliable and valid self-report questionnaire consists of 2 mood scales with 10 items each for the assessment of positive affect (eg, inspired, enthusiastic) and negative affect (eg, nervous, scared).[37] Lastly, because fibromyalgia is common in this patient population,[14,18,20] level of functioning was determined by the global score from the Fibromyalgia Impact Questionnaire (FIQ). The FIQ is a 19-item self-report instrument with a mean of 50 and SD of 10, where higher scores indicate worse functioning.[38] A version of the FIQ modified for Lyme disease patients was used.[39]

Statistical Analyses

In most cases, the comparison group was compared with the larger Chronic Multisymptom Illness group consisting of all 3 conditions. Linear regression was used to analyze continuous response variables (positive affect, negative affect, catastrophizing, and functioning), while logistic regression was used for binary responses (group membership, presence of clinical and personality disorders) and Poisson regression was used for the response of symptom number. Age and sex were used as covariates in all analyses, with the consequence that estimated differences and odds ratios are adjusted for age and sex. For secondary analyses, Tukey's pairwise comparison method was used to compare subgroups. Variables in the predictive model were determined a priori, so no model selection was performed. Somers' Dxy rank correlation[40] was used to summarize the predictive capability of the model; 0.0 corresponds to no better than random predictions within discordant pairs, while 1.00 corresponds to perfect predictions. *P*-values and confidence intervals are not adjusted for multiple testing. The R statistical environment was used for analysis,[41] while the SPSS program (SPSS Inc., Chicago, Ill) was used for recording data and generating tables.

RESULTS

Demographic and Clinical Characteristics

Forty-six (19.2%) of the 240 patients evaluated had an active infection with *B. burgdorferi* at assessment. At follow-up, 6 reported persistent symptoms and were classified as Post Lyme Disease Syndrome; another 25 of the 240 patients had been previously diagnosed and treated by other physicians and also were designated as Post Lyme Disease Syndrome (n = 31). Seventy-two (30%) of the 240 patients presented primarily with musculoskeletal complaints related to fibromyalgia, while 42 (17.5%) had medically unexplained symptoms. Most patients (60.4%) were categorized as having Chronic Multisymptom Illness. Our comparison group consisted of the 40 patients who recovered from Lyme disease after treatment, 53 patients who had an identifiable medical condition other than fibromyalgia explaining the symptoms, and 2 completely healthy patients concerned about possible exposure (Table 2). Table 3 shows patient demographic and clinical characteristics by group.

Table 2 Comparison Group Diagnoses (n = 95)

	Frequency	Percent
Recovered from Lyme disease	40	42.1
Osteoarthritis	9	9.5
Neuropathy	7	7.4
Rheumatoid arthritis	7	7.4
Multiple sclerosis	6	6.3
Infection other than Lyme	4	4.2
Patellofemoral joint disease	4	4.2
Psoriatic arthritis	3	3.2
Healthy	2	2.1
Hypermobility	2	2.1
Sleep disorder	2	2.1
Systemic lupus erythematosus-like illness	1	1.1
Polymyalgia rheumatica	1	1.1
Undifferentiated connective tissue disorder	1	1.1
Parkinson's disease	1	1.1
Encephalopathy	1	1.1
Obstructive sleep apnea	1	1.1
Impingement syndrome	1	1.1
Age-related myalgia	1	1.1
Inflammatory joint disorder	1	1.1

Symptoms, Physical Examination, and Inappropriate Antibiotic Treatment

In a secondary analysis, the 2 subgroups of the comparison group did not differ significantly (Tukey's pairwise comparisons) on any of the primary outcomes. Similarly, the 3 Chronic Multisymptom Illness subgroups did not differ significantly among themselves on any of the primary outcomes. Patients in the Chronic Multisymptom Illness groups reported 47% more physical symptoms than did the comparison group ($P < .001$; 95% confidence interval [CI], 33%-62%) with Chronic Multisymptom Illness patients commonly reporting pain (97.2%), fatigue (91.7%), poor concentration (74.5%), and sleep disturbance (75.9%). Patients in the Chronic Multisymptom Illness group had few observable clinical signs like joint inflammation (2.1%) that could be misinterpreted as indicative of Lyme disease. In Chronic Multisymptom Illness patients, equivocal test re-

Table 3 Demographics, Reported Symptoms and Antibiotic Treatment History

			Comparison Subgroups		CMI Subgroups		
Characteristic	Comparison (n = 95)	CMI (n = 145)	LD (n = 40)	Medical (n = 55)	PLDS (n = 31)	CMI-FM (n = 72)	CMI-MUS (n = 42)
Age in years: mean (SD)	45.2 (13.9)	42.6 (13.1)	43.4 (15.0)	46.5 (13.1)	42.4 (4.1)	40.8 (12.7)	44.6 (12.5)
Male sex – n (%)	37 (38.9)	41 (28.3)	20 (50.0)	17 (30.9)	14 (45.2)	8 (11.1)	19 (45.2)
White race – n (%)	86 (90.5)	127 (87.6)	36 (90.0)	50 (90.9)	29 (93.5)	60 (83.3)	38 (90.5)
Full-time employment – n (%)	48 (50.5)	63 (43.4)	17 (42.5)	31 (56.4)	12 (38.7)	29 (40.3)	22 (52.4)
High-school graduate – n (%)	93 (97.9)	141 (97.2)	40 (100.0)	54 (98.2)	30 (96.8)	72 (100.0)	39 (92.8)
College graduate – n (%)	54 (56.8)	68 (46.9)	22 (55.0)	32 (58.2)	13 (41.9)	31 (43.1)	24 (57.1)
Household income <$60,000 – n (%)	33 (34.7)	68 (46.9)	14 (35.0)	19 (34.5)	14 (45.1)	40 (55.5)	14 (33.3)
Married – n (%)	68 (71.6)	84 (57.9)	31 (77.5)	37 (67.3)	22 (71.0)	37 (51.4)	25 (59.5)
Patient reported:							
Number of symptoms: mean (SD)	5.9 (3.3)	8.7 (3.4)	6.5 (3.6)	5.5 (3.0)	8.7 (3.4)	9.4 (3.4)	7.9 (3.4)
Pain – n (%)	84 (88.4)	141 (97.2)	35 (87.5)	49 (89.1)	30 (96.8)	71 (98.6)	40 (95.2)
Fatigue – n (%)	69 (72.6)	133 (91.7)	32 (80.0)	37 (67.3)	29 (93.5)	68 (94.4)	36 (85.7)
Poor concentration – n (%)	45 (47.4)	108 (74.5)	23 (57.5)	22 (40.0)	24 (77.4)	57 (79.2)	27 (64.3)
Sleep disturbance – n (%)	44 (46.3)	110 (75.9)	20 (50.0)	24 (43.6)	24 (77.4)	60 (83.3)	26 (61.9)
Physician-observed joint inflammation – n (%)	13 (13.7)	3 (2.1)	7 (17.5)	6 (10.9)	1 (3.2)	2 (2.8)	—
Duration of illness – median in months	4	18	3	8	8	24	24
Positive ELISA – n (%)	35 (36.8)	40 (27.6)	26 (65.0)	9 (16.4)	21 (67.7)	13 (18.1)	6 (14.3)
Positive Western Blot – n (%)	29 (30.5)	34 (23.4)	24 (60.0)	5 (9.1)	22 (71.0)	8 (11.1)	4 (9.5)
Any antibiotic – n (%)	75 (78.9)	109 (75.2)	40 (100.0)	35 (63.6)	30 (96.8)	51 (70.8)	28 (66.7)
Oral antibiotic – n (%)	67 (70.5)	96 (66.2)	35 (87.5)	32 (58.2)	23 (74.2)	47 (65.3)	26 (61.9)
Multiple oral antibiotics – n (%)	25 (26.3)	45 (31.0)	11 (27.5)	14 (25.5)	10 (32.3)	23 (31.9)	12 (28.6)
IV/IM antibiotic – n (%)	15 (15.8)	43 (29.7)	12 (30.0)	3 (5.5)	13 (41.9)	17 (23.6)	13 (31.0)
Multiple IV/IM antibiotics – n (%)	1 (1.1)	14 (9.7)	1 (2.5)	—	2 (6.5)	6 (8.3)	6 (14.3)

CMI = Chronic Multisymptom Illness; LD = Lyme disease; PLDS = Post Lyme Disease Syndrome; FM = fibromyalgia; MUS = multiple unexplained symptoms; ELISA = enzyme-linked immunosorbent assay; IV = intravenous; IM = intramuscular.

sults, unreliable tests (eg, Lyme urine antigen test), or unproven laboratories appeared to contribute heavily to previous misdiagnosis.

Although 169 (70.4%) patients at no time met criteria for Lyme disease, 114 (67.5%) of them had received at least one course of oral or intravenous antibiotics. Thirty-three (28.9%) of the 114 patients received multiple courses of oral antibiotics, while intravenous antibiotics were provided for 22 patients, with 12 receiving repeated intravenous antibiotic treatment often over a period of months or years. Nineteen (35.8%) of the 53 comparison group patients with medical conditions (not Lyme disease) received antibiotic treatment, with 9 receiving multiple courses of antimicrobials.

Psychiatric Co-Morbidity

Twenty (21.1%) patients in the comparison group met criteria for a clinical disorder (Table 4). Conversely, clinical disorder rates were significantly higher for patients in the Chronic Multisymptom Illness groups ($P < .001$; odds ratio 3.54, 95% CI, 1.97-6.55); the highest rate was observed in the fibromyalgia group (52.8%). Current major depressive disorder and generalized anxiety disorder were the most commonly observed psychiatric disorders. Somatization disorder occurred at comparatively low rates across groups, although the rate for patients with fibromyalgia (13.9%) was slightly elevated.

Personality disorders occurred at the highest rate in fibromyalgia group (38.9%); however, the difference between the Chronic Multisymptom Illness groups and the comparison group was not significant. Histrionic personality disorder was observed in 19.4% of fibromyalgia patients (Table 4).

Associated Cognitive, Affective and Functional Outcomes

Chronic Multisymptom Illness patients were more likely than comparison group patients to have lower levels of positive affect ($P < .001$, mean difference −4.3, 95% CI, −6.4 to −2.2), higher levels of negative affect ($P < .001$, mean difference +3.7, 95% CI, 1.7-5.7) and a greater tendency to catastrophize pain ($P < .001$, difference of 5.8, 95% CI, 3.0-7.8). The Chronic Multisymptom Illness group had worse functioning scores than did the comparison group ($P < .001$; increase of 15.1, 95% CI, 10.3-19.9) and these scores were related to catastrophizing ($r = .522$, $P < .001$), negative affect ($r = .483$, $P < .001$) and positive affect ($r = -.342$, $P < .001$). Lastly, clinical disorders were pre-

Table 4 Psychiatric Co-Morbidity, Other Psychological Factors and Functioning

			Comparison Subgroups		CMI Subgroups		
	Comparison (n = 95)	CMI (n = 145)	LD (n = 40)	Medical (n = 55)	PLDS (n = 31)	CMI-FM (n = 72)	CMI-MUS (n = 42)
Any clinical disorder – n (%)	20 (21.1)	71 (48.9)	9 (22.5)	11 (20.0)	15 (48.4)	38 (52.8)	18 (42.9)
Depression – current – n (%)	6 (6.3)	42 (29.0)	2 (5.0)	4 (7.3)	14 (45.2)	17 (23.6)	11 (26.2)
Depression – past – n (%)	2 (2.1)	6 (4.1)	1 (2.5)	1 (1.8)	1 (3.2)	5 (6.9)	—
Depression – dysthymia – n (%)	3 (3.2)	14 (9.7)	2 (5.0)	1 (1.8)	5 (16.1)	5 (6.9)	4 (9.5)
Anxiety disorder – n (%)	13 (13.8)	40 (27.6)	6 (15.0)	7 (12.7)	9 (29.0)	20 (27.8)	11 (25.6)
Panic disorder – n (%)	5 (5.3)	21 (14.8)	3 (7.5)	2 (3.6)	4 (12.9)	10 (13.9)	7 (16.3)
Generalized anxiety disorder – n (%)	11 (11.6)	28 (19.3)	5 (12.5)	6 (10.9)	8 (25.8)	13 (18.1)	7 (16.7)
Post-traumatic stress disorder – n (%)	—	1 (0.7)	—	—	—	1 (1.4)	—
Social anxiety disorder – n (%)	—	2 (1.4)	—	—	—	1 (1.4)	1 (2.4)
Somatization disorder – n (%)	2 (2.1)	13 (9.0)	—	2 (3.6)	2 (6.5)	10 (13.9)	1 (2.4)
Undifferentiated somatization disorder – n (%)	—	7 (4.8)	—	—	1 (3.2)	4 (5.6)	2 (4.8)
Pain disorder – n (%)	4 (4.2)	17 (11.7)	3 (7.5)	1 (1.8)	3 (9.7)	11 (15.3)	3 (7.1)
Substance abuse disorder – n (%)	1 (1.1)	1 (0.7)	1 (2.5)	—	1 (3.2)	—	—
Eating disorder – n (%)	1 (1.1)	4 (2.8)	1 (2.5)	—	—	2 (2.8)	2 (4.8)
Any personality disorder – n (%)	20 (21.1)	47 (32.4)	11 (27.5)	9 (16.4)	9 (29.0)	28 (38.9)	10 (23.8)
Histrionic – n (%)	3 (3.2)	17 (11.7)	1 (2.5)	2 (3.6)	—	14 (19.4)	3 (7.1)
Narcissistic – n (%)	8 (8.4)	11 (7.6)	3 (7.5)	5 (9.1)	2 (6.5)	6 (8.3)	3 (7.1)
Compulsive – n (%)	7 (7.4)	6 (4.1)	5 (12.5)	2 (3.6)	1 (3.2)	3 (4.2)	2 (4.8)
Dependent – n (%)	1 (1.1)	4 (2.8)	1 (2.5)	—	2 (6.5)	2 (2.8)	—
Depressive – n (%)	—	3 (2.1)	—	—	2 (6.5)	—	1 (2.4)
Schizoid – n (%)	—	3 (2.1)	—	—	1 (3.2)	1 (1.4)	1 (2.4)
Masochistic – n (%)	—	1 (0.7)	—	—	1 (3.2)	—	—
Avoidant – n (%)	—	1 (0.7)	—	—	—	1 (1.4)	—
Other – n (%)	1 (1.1)	1 (0.7)	1 (2.5)	—	—	1 (1.4)	—
Functioning – mean (SD)	38.9 (19.3)	54.2 (17.8)	38.5 (19.3)	39.0 (19.3)	55.9 (19.1)	56.3 (16.9)	49.7 (17.9)
Negative affect – mean (SD)	19.1 (7.3)	23.0 (7.9)	19.8 (8.3)	18.7 (6.4)	25.0 (9.3)	23.0 (7.3)	21.6 (7.6)
Positive affect – mean (SD)	34.0 (7.0)	29.6 (8.4)	33.0 (7.2)	34.7 (6.8)	28.6 (7.4)	29.5 (8.4)	30.6 (9.1)
Catastrophizing – mean (SD)	6.5 (6.6)	12.6 (8.2)	5.8 (5.3)	7.0 (7.4)	13.1 (8.0)	13.6 (8.1)	10.8 (8.3)

CMI = Chronic Multisymptom Illness; LD = Lyme disease; PLDS = Post Lyme Disease Syndrome; FM = fibromyalgia; MUS = multiple unexplained symptoms.

dictive of worse functioning scores for all patients ($P < .001$, difference of 21.6, 95% CI, 17.1-26.1).

Explanatory Model

The hypothesized prediction model consisting of age, sex, clinical disorders, personality disorders, catastrophizing, positive affect, and negative affect adequately accounted for group inclusion (Table 5; $P < .001$ compared with a base model of age and sex only), with a Somers' Dxy rank correlation of .53. Catastrophizing, positive affect, and personality disorders all significantly contributed to the model after accounting for other effects, with odds ratios for the Chronic Multisymptom Illness groups of 2.09, 0.64, and 2.35, respectively, for an increase of 10 on the catastrophizing scale, an increase of 10 on the positive affect scale, or the presence of a personality disorder.

It is worth noting that although the clinical disorder rate differed significantly between groups (Chronic Multisymptom Illness and comparison) while the personality disorder rate did not, as discussed above, in the predictive model the opposite was true with regard to significance. As the tests in the predictive model can be thought of as adjusting for the other terms, these results reflect the relations among the terms in the predictive model and suggest the importance of considering several measures simultaneously.

Table 5 Predictive Model for Chronic Multisymptom Illness

Factor	*P* Value	Odds Ratio	95% CI for OR
Age	.68	0.95	(0.76-1.20)
Sex	.67	0.86	(0.44-1.69)
Catastrophizing	.005	2.09	(1.25-3.47)
Negative Affect	.71	1.10	(0.67-1.82)
Positive Affect	.04	0.64	(0.41-0.98)
Clinical Disorders	.08	1.96	(0.93-4.12)
Personality Disorders	.02	2.35	(1.15-4.82)

CI = confidence interval; OR = odds ratio.

Odds ratios for Age, Catastrophizing, Positive Affect, and Negative Affect are based on a change of 10 units. Sex effect is for female.

DISCUSSION

Our data supported previous observations that the chronic symptoms of most patients presenting to academic Lyme disease referral centers cannot be attributed to ongoing infection with *B. burgdoferi*.[14,19,20] While some of our patients had another medical condition that explained the complaints attributed to Lyme disease, the physical, cognitive, and emotional symptoms of most patients were more consistent with Chronic Multisymptom Illness or psychiatric disorders. Almost 49% of patients in our Chronic Multisymptom Illness group had clinical disorders like Major Depressive Disorder or Generalized Anxiety Disorder, in contrast to the comparison group with a rate of 21.1%, which is closer to the rate observed in the general population, 26.2%.[42] In addition, psychological factors associated with poor medical outcomes including catastrophizing, high negative affect, and low positive affect were more pronounced in Chronic Multisymptom Illness than in the comparison group. A model based on psychiatric co-morbidity and these 3 psychological factors predicted the likelihood that a patient would be included in a Chronic Multisymptom Illness group. Moreover, the presence of clinical disorders, catastrophizing, high negative affect, and low positive affect were highly related to poor functioning.

We did not find personality disorders to be predictive of Chronic Multisymptom Illness group inclusion, although 2 of 3 Chronic Multisymptom Illness groups had elevated rates (Post Lyme Disease Syndrome = 29.0% and fibromyalgia = 38.9%) not seen in the comparison group (21.1%) or in the general population (~9%).[43] Of interest, the presence of personality disorders did contribute significantly to our predictive model, which emphasizes the importance of considering the relationships among several variables at once. However, our instrument is known to produce a high rate of false positives and, despite our efforts to control for this, false positives could have been a problem herein. Others have found lower rates of personality disorders in fibromyalgia (8.7%).[44] Despite these caveats, Lamberg noted that personality disorder is frequently present in some of our most "difficult" medical patients whether their symptoms are medically explained or not.[45] Conversely, half of our Chronic Multisymptom Illness patients did not meet criteria for psychiatric co-morbidity, which is consistent with other reports describing subgroups of psychologically healthy fibromyalgia patients who in one study reported lower levels of pain despite increased pain sensitivity.[46]

Chronic Multisymptom Illness patients had 47% more symptoms than the comparison patients, and medicalizing these symptoms has adverse consequences for Chronic Multisymptom Illness patients. When attributing symptoms to an infectious disease, unnecessary antibiotic treatment is often given. Almost 68% of our patients with no evidence of Lyme disease received antibiotic treatment; 29% of them received multiple antimicrobials for months or even years. Baker recently argued that despite convincing results otherwise, some maintain that "chronic Lyme disease" is the result of a persistent infection with *B. burgdorferi*, requiring several months of antibiotic therapy, which is an unprecedented treatment approach for a non-life-threatening disease.[47] Antibiotics are unique in that their use affects the patient to whom they are prescribed as well as future patients through the generation of new antibiotic-resistant strains of bacteria.[48,49]

Our study was limited by the cross-sectional design, thus it is inappropriate to infer causality. Depression and poor affect could be the result of living with chronic symptoms instead of being predisposing factors. Longitudinal studies assessing psychological factors in newly diagnosed Lyme disease patients followed over time could better address these questions. Our comparison group consisted of patients with a variety of medical conditions, which likely results in varying levels of psychiatric comorbidity. Future studies would benefit from evaluating a more homogenous comparison group, for example, only osteoarthritis patients. Also, the accurate assessment of the variables of interest was limited by our questionnaires despite selecting most for their "gold standard" status. Lastly, our Chronic Multisymptom Illness patients may not be representative of others who never ascribed symptoms to "chronic Lyme disease" and received antibiotic treatment.

In conclusion, psychiatric comorbidity and other psychological factors are prominent in the presentation and outcome of some patients who inaccurately ascribe longstanding symptoms to "chronic Lyme disease." Less than 20% of patients presenting to our Lyme disease specialty center had a current infection with *B. burgdorferi.* Most patients had other medical conditions or Chronic Multisymptom Illness, but were being treated with antibiotics for Lyme disease. Depression and anxiety disorders were common in Chronic Multisymptom Illness patients, as were other psychological factors, for example, negative affect and catastrophizing, associated with poor functional outcomes. Our findings suggest that multidisciplinary treatment addressing the physical and often emotional suffering of such patients will be more effective than perpetuating the diagnosis of "chronic Lyme disease."

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