Post Lyme Syndrome: Contrasts with Recovered Lyme Patients on Cognitive and Symptom Measures

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ABSTRACT

Post Lyme syndrome (PLS) is defined by symptom persistence following treatment of documented Lyme disease. Many of PLS symptoms suggest disturbance of the central nervous system (CNS). To further define this disorder and CNS effects, we compared 39 patients with PLS and 16 patients who recovered from Lyme disease on a quality of life inventory, symptom measures, and psychiatric interview. The two patient groups were also compared to healthy controls on a Lyme neuropsychological battery. Patients with PLS compared to recovered Lyme (RL) patients showed significant reductions in perceived health ($P < .001$), physical and role functioning ($P < .001$), social functioning ($P < .01$), elevated pain ($P < .01$), fatigue ($P < .01$), and disturbed sleep ($P < .01$) but did not differ in the life-time frequency of affective disorders. Relative to healthy controls, patients with PLS but not with RL showed deficits on measures of verbal memory $P < .05$), verbal fluency ($P < .05$), attention ($P < .01$), and motor speed ($P < .01$). This study suggests that strategies aimed at symptom reduction, enhanced cognitive performance, and improved quality of life are critically important for this group of patients.

Key words: Lyme disease, encephalopathy, depression, quality of life

INTRODUCTION

Lyme disease, the most frequent vector borne infection in the United States,[1,2] is a multisystemic disorder caused by the spirochete *Borrelia burgdorferi*. When Lyme disease is associated with localized infection and promptly treated, its course is often self-limited.[3] However, in patients with disseminated disease or in cases where diagnosis and treatment are delayed, major necrologic and psychiatric sequella can develop and persist post-treatment.[6-13] However, the relation between the cognitive, sleep, and psychiatric abnormalities and the infection are controversial as is appropriate management.[4,5]

This study sought to clarify the symptoms associated with chronic Lyme disease by focusing on a clearly defined patient group, those who met criteria for post Lyme syndrome (PLS). Post Lyme syndrome is defined as documented Lyme disease associated with persistent symptoms six or more months post treatment.[14] Patients with PLS and two comparison groups underwent extensive evaluation to define the interrelation between cognitive impairments, psychological status and physical symptoms.

METHODS

Included in the study were 39 patients with PLS, 16 recovered Lyme disease (RL) patients, and 45 nonpatient healthy controls. PLS and RL patients were recruited from the Stony Brook University Hospital Lyme disease center and outpatient neurology practices, direct referrals from private practices in the tristate area (New York, New Jersey, Connecticut), and local community physicians seeking a second opinion regarding chronic Lyme disease.

All PLS and RL patients had documented histories of Lyme disease and were seropositive for *B burgdorferi* by ELISA and Western blot as performed at Stony Brook University Hospital laboratory. Patients from both groups had completed at least three weeks oral or parenteral antibiotic treatment for Lyme disease as currently recommended in review articles and practice guidelines.[1,2] All subjects had completed antibiotic therapy six or more months prior to evaluation.

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Post Lyme Syndrome Patients

There were 31 of the 39 patients with PLS who had Lyme disease histories amd met CDC surveillance criteria for Lyme disease.[15] The remaining 8 patients had histories of *B burgdorferi* infection and were diagnosed with Lyme disease by physicians with expertise in the disease. Of these 8 patients, 2 patients seroconverted from negative to positive for *B burgdorferi* antibodies during their acute illness. The other 6 were seropositive patients who developed arthralgia, myalgia, fever, and meningeal symptoms. Specific Lyme manifestations in the PLS sample included: documented erythema migrans (EM;16/39), cranial neuropathy (10/39), joint swelling (17/39), and meningitis (2/39). All patients with PLS complained of severe fatigue that had an onset that corresponded to their Lyme disease and reported good to excellent health prior to developing Lyme disease. Fatigue severity was measured with the Fatigue Severity Scale (FSS),[16] a 9-item scale with scores ranging from 1.0 (no fatigue) to 7.0 (severe fatigue). All PLS patients scored > 4.0. Some of the psychometric findings on a subset of these patients and healthy controls has been previously reported.[17]

Recovered Lyme Patients

Patients with RL disease met full CDC criteria in 16/16 of cases and considered themselves to be recovered. Their histories had the following specific Lyme manifestations: EM (14/16), cranial neuropathy (5/16), and migratory arthritis with observed joint swelling (5/16). Patients with RL reported no current fatigue and all scored 3.0 or less on the FSS.

Healthy Controls

For an additional comparison group, healthy volunteers from the community were recruited by advertisements in local papers. Potential subjects were screened by telephone interviews and excluded if they reported a history of tick bite, were known to have positive serologies for *B burgdorferi* exposure, or had either Lyme disease or any other significant medical or psychiatric illness.

Inclusion criteria for all subjects were: 1) English as primary language, 2) completion of at least 10 years of education, and 3) an eighth-grade reading level or above. Exclusion criteria for all subjects were history of learning disorder or history of head trauma.

Measures

Symptom inventories. Patients with PLS and RL completed several self-report measures of relevant symptoms. For a general measure of health perceptions and quality of life, they completed the Medical Outcome Survey-Short Form (24, abbreviated form of the SF-36),[18] a 24-item questionnaire with 6 subscales: pain, physical functioning, role functioning, social functioning, mental health, and perceived health. The SF-24 has well established reliability and validity and is widely used in medical populations.[1] As noted above, fatigue was measured by the FSS and was part of the group inclusion criteria. The FSS has been shown to be reliable and identifies severe fatigue in a variety of illnesses.[16] The Rand Vitality Index,[18] a 4-item measure with scores inversely related to those from the FSS, was also included as a measure of energy level. To provide an index of subjective cognitive impairment, subjects were asked to rate their cognitive complaints as "none," "mild," "moderate," or "severe" as part of a general inventory of Lyme-related symptoms (Coyle PK, Krupp LB, unpublished data, 1997). Patients who reported problems with concentration or memory as moderate or severe symptoms were considered to have a positive response. Sleep disturbance was measured with a 9-item short form of the St. Mary's Sleep questionnaire[20] (modified to provide a numerical score) addressing the subjective experience of the preceding night's sleep. Depressive symptoms were measured by the Center for Epidemiologic Studies Depression Scale (CES-D),[21] a 20-item measure commonly used as a screening tool in medical populations (with a cut-off score of 16 or greater considered to indicate the possibility of depression). As a more general index of psychological distress, the Brief Symptom Inventory (BSI),[22] a 50-item measure assessing a variety of psychiatric symptoms, was also administered. The global symptom severity score was derived from the sum of the items according to published guidelines.[22]

Psychiatric interview. Of the 39 patients with PLS 37 patients and all patients with RL completed a structured psychiatric interview (Structured Clinical Interview for DSM-III-R or SCID; nonpatient version)[23] to establish current and lifetime incidences of DSM-III-R Axis I diagnoses. All interviews were conducted on the day of neuropsychological evaluation by a Masters-level psychologist who had completed training in SCID administration.

Neuropsychological evaluation. All subjects completed a large battery of standardized neuropsychological tests administered by a trained psychologist. The testing battery lasted approximately 2fi to 3 hours, and patients were provided with rest periods as needed.

The premorbid level of cognitive ability was estimated by the vocabulary subtests of the WAIS-R[24] and the reading subtest of the Wide Range Achievement Test-revised (WRAT-R; also used to determine study eligibility as above).[25] Next, two approaches were taken to characterize the potential cognitive deficits associated with PLS.

First, the study groups were compared along individual neuropsychological measures selected based on previous demonstrations of their sensitivity to Lyme encephalopathy.[8,14] Referred to here as the "Lyme Battery," these 9 selected measures consisted of the following: WAIS-R

Table 1. Self-reported symptoms in post Lyme syndrome and recovered Lyme controls.

	PLS (n=39)	RL (n=16)	P*
Pain#	50 (22)	80 (23)	<.01**
Fatigue	5.5 (0 9)	2.3 (1.1)	<.001
Vitality#	11.4 (3.8)	19.4 (2.0)	<.001
Depressive symptoms	17.5 (9.3)	4.1 (3.9)	<.001
Cognitive impairment#	55%	12%	<.01
Sleep disturbances	7 (6.7)	13.8 (3.1)	<.001
Current psychiatric diagnoses **	7/37 (19%)	1/16 (6%)	ns
Lifetime psychiatric diagnoses***	12/37 (32%)	2/16 (12%)	ns

Compared by student t test unless otherwise indicated; **compared by Mann Whitney U test; * compared by Fisher exact test, measured by the pain subscale of the SF-24 [normative range 80-100], measured by the FSS [normative mean 2.1], measured by the Rand Vitality Index, measured by the CES-D [normative mean 6.7], measured by the total symptom scores of the BSI, measured by the Lyme symptom checklist, measured by modified version of the St Mary's Sleep questionnaire; #On these questionnaires missing data on some patients led to a sample size of 34-36 on PLS cases and 13-15 on RL cases; *Since 2 patients did not undergo the entire psychiatric interview because of scheduling difficulties, their data were not included.*

Digit Span (attention),[24] Trail Making Parts A and B (visuomotor search),[26] Controlled Oral Word Association (COWA; verbal fluency),[27] Finger Tapping Test (fine motor speed),[26] Selective Reminding Test (SRT), 6 trial version (verbal learning and memory; sum recall and continuous long-term retrieval measures),[28] Logical Memory subtest of the Wechsler Memory Scale-Revised (verbal memory; immediate recall score),[29] and the Benton Visual Retention Test (BVRT; total number of errors).[30]

The second approach was to compare the study groups along one global rating of cognitive impairment. To obtain these ratings, a summary of test scores for each subject was provided to a clinical neuropsychologist (DM) along with the subject's age and years of education. Blind to diagnosis, he rated each of the profiles by determining the number of test scores that fell below the estimated level of premorbid functioning. Impairment was defined as the presence of four or more scores, one SD below estimated premorbid level of ability, or three or more tests two SD below estimated premorbid level of ability. This rating approach has been used in a variety of clinical populations and shown to be both sensitive and useful in comparisons of cognitive performance with other laboratory measures (eg, neuroimaging).[31]

RESULTS

Demographic Characteristics

The PLS patients had a mean of 44 (14.0) years of age, an average of 15 ± 2.3 years of education, and were 59% women. The RL patients had a mean of 50 ± 14.0 years of age, 15 ± 2.5 years of education, and were 35% women. Healthy controls had a mean of 46 ± 14.0 years of age, 15 ± 1.9 years of education, and were 71% women. Patients with PLS, RL, and the healthy controls significantly differed according to gender (more woman in PLS group), but not according to age or years of education.

Table 2. Quality of life/perceived health in post Lyme and recovered Lyme disease.

	Post Lyme (n)	Recovered Lyme (n)	P Value
Quality of life measure	35	14	
Physical functioning	66	95	<.001
Role functioning	58	98	<.001
Social functioning	65	99	.008
Mental health	74	92	ns
Perceived health	48	89	<.001

Symptom Inventories

As shown in Table 1, the PLS and RL patients significantly differed on many of the symptom measures. PLS patients reported more sleep disturbances ($P < .001$), more depressive symptoms ($P < .001$), less vitality ($P < .001$), more pain ($P < .01$), greater psychological distress ($P < .001$), and more complaints of cognitive difficulty ($P < .01$). As shown in Table 2, compared to the patients with RL, patients with PLS also reported reduced quality of life on 5 of the 6 subscales of the SF-24 (physical functioning, $P < .01$; role functioning, $P < .01$; social functioning, $P < .01$; and perceived health, $P < .01$), with mental health functioning as the exception.

Psychiatric Diagnoses

There was not a significant difference between the PLS and RL patients in current or lifetime incidences of psychiatric diagnoses (shown in Table 1). In patients with PLS, 7 (19%) met current criteria for current DSM-III-R Axis I disorders: major depression (n=4), dysthymia (n=1), panic disorder (n=1), and social phobia (n=1). Patients with RL (6%) met current criteria for major depression. Lifetime criteria for Axis I disorders were met by 32% of patients with PLS and 12% of patients with RL.

Cognitive Functioning

Results of neuropsychological testing are shown in Table 3. There were no significant differences between the groups in estimated premorbid level of functioning (WAIS-R Vocabulary subtest and WRAT-R Reading subtest).

As shown in Table 3, the mean scores of the PLS patients on the measures of the Lyme Battery indicated

Table 3. Cognitive functioning in post Lyme syndrome, recovered Lyme, and non-patient healthy controls.

TEST	Post Lyme Syndrome Mean SD	Recovered Lyme Mean SD	Healthy Controls Mean SD	PLS vs Healthy Controls *P* Value
Premorbid Measures				
WRAT-R reading	74.3 (10.2)	73.2 (9.6)	70.81 (8.7)	.12
WAIS-R vocabulary	11.7 (3.2)	12.8 (2.8)	12.1 (2.3)	.22
Lyme Battery				
Digit span	15.1 (4.1)	16.3 (4 9)	17.3 (3 7)	<.01
SRT sum of recall	47.3 (8.5)	47.7(10.8)	52.1 (6.3)	<.01
SRT consistent recall	26.4 (12.2)	33.0 (16.4)	31.9 (13.3)	.07
Logical memory (immediate recall)	23.6 (7.3)	26.6 (5.4)	27.1 (6.0)	.02
Trail makinq part A	30.4 (2.4)	27.3 (10.6)	29.0 (14.8)	.18
Trail making part B	75.1 (33.5)	65.7 (27.7)	66.3 (23.8)	.13
Verbal fluency (COWA)	38.8 (12.3)	43.2 (12 9)	45.6 (10.9)	.02
Finger tapping (dominant hand)	48.3 (10.2)	51.9 (11.8)	55.1 (10.2)	<.01
Benton visual Retention (errors)	2.7 (1.4)	2.1 (1.4)	2.2 (1.4)	.12

Compared by logistic regression controlling for age and education, only significant differences between PLS vs HO are shown; #Digit Span is from the WAIS-R, Sum of Recall and Consistent Recall are measures of the Selective Reminding Test (6 trial version), Logical Memory is from the Wechsler Memory Scale-Revised, Trail Making Parts A and B, and Finger Tapping are measures from the Halstead-Reitan Battery, Benton # errors is from the Benton Visual Retention Test.

consistently poorer performances relative to both comparison groups. These differences were significant between the PLS and healthy controls on 6 of 9 measures: WAIS-R Digit Span ($P < .01$); SRT sum of recall ($P < .01$); WMS-R Logical Memory ($P < .05$); COWA ($P < .05$); and finger tapping ($P < .01$). (Repeated analyses excluding the 8 PLS patients whose histories did not meet full CDC surveillance criteria for Lyme disease did not alter the significance of these results.) There were no significant differences between the PLS and RL groups or the RL and healthy controls.

Based on the clinical ratings described above, global cognitive impairment was identified in 58% of PLS patients, 25% of RL, and 11% of the healthy controls. Again, this difference was significant between the PLS and healthy controls ($P < .001$).

Inter-relationships Between Symptoms and Cognitive Functioning

Correlational analyses were performed on self-report data from the patients with PLS and RL and neuropsychological measures to explore possible associations. Neither sleep, depression, or fatigue was significantly correlated with the 6 neuropsychological measures that distinguished PLS and nonpatient controls. Pain was significantly correlated with SRT sum or recall ($r = .39$, $P = .02$), but not the other 5 cognitive measures.

DISCUSSION

The current findings indicate that PLS is characterized by a mild to moderate encephalopathy with relative deficits in measures of attention and verbal memory. These deficits can not be attributed to depression.

Several other studies have also documented cognitive dysfunction in untreated and partially treated patients with Lyme disease. For example, Benke et al demonstrated that disseminated Lyme and PLS cases have deficits in executive functioning, verbal fluency, and verbal memory.[7] Other studies have demonstrated deficits in Lyme cases compared to subjects with depression and fibromyalgia.[10] Bujak found deficits in patients with PLS compared to a group of recovered Lyme patients.[14]

Unique to the current investigation was our exclusive focus on well defined post-treatment cases and the addition of an extensive psychological and physical symptom evaluation to the Lyme cognitive battery. Using a global rating, more than half of PLS cases met criteria for cognitive impairment. Another striking finding was the extent to which PLS patients reported impairments in quality of life. Based on the SF-36, patients with PLS indicated impaired physical functioning, social functioning, and perceived health compared to the patients with RL. Patients with PLS also reported greater sleep disturbances, cognitive loss, more pain, and heightened psychological distress compared to patients with RL. In fact it is their perception of poor

health attributed to Lyme disease that is one of the most salient features of the PLS group. While they do show greater global impairment relative to patients with RL, they did not significantly differ on the specific measures of the Lyme battery compared to the RL patients. Nonetheless, PLS patients perceived significantly greater cognitive difficulty relative to the RL group based on a subjective report.

Perceived poor health is often a characteristic of elevated psychological distress and in fact 2 measures of psychological distress, the CES-D and BSI global symptom severity score were elevated in PLS compared to the RL patients. However, despite these significant group differences, there was not a significant group difference in current or lifetime incidence of DSM-III-R Axis I disorders, including major depression. Therefore, affective disorders alone can not be used to explain the elevated psychological distress nor the encephalopathy. That the psychological state of patients with PLS is linked in part to their somatic manifestations of fatigue, pain, and sleep disturbance is supported by the findings on the SF-36 in which all subscales of quality of life were impaired in the PLS group except mental functioning.

This study suggests that fatigue and associated symptoms of malaise are severe in PLS. Fatigue is also a prominent problem in CFS. However, as recently demonstrated by Gaudino et al,[17] the frequency of a lifetime psychiatric history of affective disorder is somewhat higher in CFS[32] than PLS while cognitive deficits appear more pronounced.

While prospective studies are in progress to explore the relative contribution of infectious, immune, and psychological factors in PLS, this study suggests that strategies aimed at symptom reduction and improved quality of life are critically important for this group of patients.

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