Repeated Antibiotic Treatment in Chronic Lyme Disease

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ABSTRACT

Patients with chronic Lyme disease who experience persistent cognitive deficits despite having received the recommended antibiotic treatment pose a therapeutic dilemma. This pilot study was designed to assess whether additional antibiotic therapy is beneficial.

Enrolled in the study were 23 patients with complaints of persistent memory problems who had previously received 4-16 weeks of intravenous antibiotic therapy. Patients were tested at baseline and 4 months later. During this interval, the private physician determined treatment (intravenous, intramuscular, oral, or none). Assessments included standardized measures of cognition, depression, anxiety, and functional status.

Between times 1 and 2, 5 patients were given no antibiotics and 18 were given additional antibiotics: 7 intravenously, 4 intramuscularly, and 7 orally. At time 1, there were no statistically significant group differences in cognition, depression, or anxiety between those who later received antibiotics and those who didn't. At time 1, the 23 patients were also functionally disabled. At time 2, compared with patients who received no antibiotics, patients given antibiotics scored better on overall and individual measures of cognition. Patients given intravenous antibiotics showed the greatest functional improvement (pain, physical functioning, energy) and the most cognitive improvement, even when controlling for baseline differences in cognition between the treatment groups. Patients who did not have a reactive Western blot currently or historically were just as likely to improve cognitively as patients with reactive Western blot results.

This uncontrolled study suggests that repeated antibiotic treatment can be beneficial, even among patients who have been previously treated and even among patients who are currently Western blot negative, with the intravenous route of treatment being the most effective. A double-blind placebo-controlled study is needed to confirm these results.

Key words: encephalopathy, Lyme disease, treatment

INTRODUCTION

Lyme disease, caused by infection with the spirochete *Borrelia burgdorferi,* can result in a chronic illness that persists despite standard courses of antibiotic therapy. Characterized by persistent fatigue, arthralgias, myalgias, peripheral neurologic disorders, and/or central neurologic problems including mild to severe encephalopathy,[1-3] chronic Lyme disease (CLD) may result in significant functional disability.[4,5]

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Two main etiologies have been invoked to explain the persistent symptoms: persistent infection and a postinfectious immunoinflammatory disorder.

The persistent infection hypothesis is based on several lines of evidence. Uncontrolled clinical case reports indicate that some patients benefit from longer and repeated courses of antibiotic therapy.[6-9] Microbiological studies have shown that, even after antibiotic therapy, persistence of the organism may be demonstrated by either culture or polymerase chain reaction analysis in animals and humans.[10-17] Further, microbiologists speculate that persistence may be promoted by the ability of *B burgdorferi* to lodge intracellularly in human endothelial cells, astrocytes, fibroblasts, and macrophages[18-23] and to modify its shape into potentially antibiotically-protected cyst-like forms.[24,25] According to the persistent infection theory, failure of antibiotic therapy result from an intracellular

location of the organism, the selection of resistant strains, or sequestration of the organism in "protected" sites, such as the central nervous system.

The postinfectious immunoinflammatory hypothesis also is supported by several lines of evidence. At least for Lyme arthritis, it has been suggested that patients who carry the HLA-DR4 or DR2 allele are more vulnerable to developing antibiotic-resistant chronic Lyme arthritis.[26] For neurologic Lyme disease, only one study reported an association with these alleles,[27] whereas other European studies were not able to find such an association.[28,29] Molecular mimicry may also account for a portion of persistent Lyme disease, but the evidence for this has been indirect, based on the observation that antibodies from patients with Lyme disease have been found to cross-react with ganglosides, myelin, and a 64-kd protein seen in normal human axons.[30-34] Flagellin protein may generate cross-reactive antibodies to myelin basic protein (eg, elevation has been seen among patients with neuroborreliosis). Finally, persistent neurologic Lyme disease may not be caused by autoimmunity but, instead, caused by the damage done by persistent activation of inflammatory cytokines by remnants of pieces of the spirochete. Elevated levels of interleukin-6, tumor necrosis factor-alpha, and nitric oxide are known to be produced by neural cells exposed to *B burgdorferi*.[35,36] These cytokines can induce many of the symptoms of fatigue and malaise associated with CLD.

Uncertainty regarding the etiology of CLD has led to considerable polarization within the medical community regarding etiology and concern over the serious consequences associated with either undertreating or overtreating patients. In view of the complexity of borreliae and the intricacy of the host-pathogen interactions, it is likely that individual patients may suffer from persistent infection, residual damage, an ongoing autoimmune reaction, or any combination of these.

Given the etiological uncertainty regarding CLD and the importance of measuring response to treatment in an objective way, in 1993 we designed an uncontrolled pilot study to determine whether patients with persistent memory complaints after the diagnosis and treatment of Lyme disease, who have been previously adequately treated, show quantitative cognitive improvement with repeated antibiotic treatment over a four-month interval.

METHODS

Patients

Institutional Review Board approval was obtained for this study from the New York State Psychiatric Institute. Prior to formal assessments, patients were interviewed by the primary investigator to confirm study eligibility and to obtain signed informed consent.

Adults age 18-65 with previously diagnosed and treated Lyme disease who complained of persistent cognitive symptoms were recruited from the offices of community physicians who practice in Lyme endemic areas. The diagnosis of Lyme disease was based on the following criteria: a) exposure to a Lyme endemic area; b) a history of a physician-diagnosed erythema migrans rash and/or a positive serological test for Lyme disease (ELISA, Western blot); and c) a history of clinical symptoms typical of Lyme disease affecting the cardiac, neurologic, and/or articular systems. To be eligible for our study, all patients had to have been previously treated with at least 4 and no more than 16 weeks of intravenous antibiotics prior to study enrollment. Because this study was designed prior to the establishment of the two-tiered serologic testing method now recommended by the Center for Disease Control and Prevention (CDC),[37] our criteria used the prior CDC standard of either a reactive ELISA or a reactive Western blot. Although some patients had cerebral spinal fluid studies done previously and/or magnetic resonance imaging scans, these studies were not requirements for study entry.

Assessments

Patients were evaluated at baseline and four months later on a battery of standardized tests. These tests evaluated disability (MOS Short-form 36 Functional Status Questionnaire), anxiety (Zung Anxiety Scale), depression (Beck Depression Inventory), and cognition (Wechsler Adult Intelligence Scale, the Wechsler Memory Scale, and the Controlled Oral Word Association Test). Between the two assessment points, patients returned to their private physician.

Neuropsychological change was assessed in two ways. First, the group's mean change between Time 1 and Time 2 on each of the neuropsychological tests was assessed. Second, a composite z-score was created for each individual by adding the number of standard deviations away from published age norms on the following 16 tests: each of the 11 subtests of the WAIS, the 4 tests of the Wechsler Memory Scale (Verbal Memory, Visual Memory, Attention/Concentration, Delayed Memory), and the Controlled Oral Word Association Test.

Serum was collected from 19 of the 23 patients for Lyme serology testing, which was sent to BBI Clinical Laboratories for analysis. Serum from 16 patients was also sent to the University Hospital of Stony Brook for *B burgdorferi*-specific immune complex assays.[38,39]

Treatment

Because this was a pilot clinical study, treatment over the four-month interval was not controlled. Patients were treated according to the clinical judgment of their physi-

Table 1. Weeks of treatment with oral, intravenous (IV), or intramuscular (IM) antibiotic prior to study entry (N = 23).

	Oral Group	IV Group	IM Group	No Antibiotic	All Groups	*P*
Prior oral antibiotics	27.6±19.2	12.7±12.5	95.8±76.0	19.8±26.2	33.2±44.2	NS
Prior IV antibiotics	11.1±13.3	8.7±3.9	9.3±4.6	4.4±1.5	8.6±7.9	NS
Prior IM antibiotics	0	0	0	0	0	NS

Abbreviation: NS = not significant.

cians. Most patients were treated with antibiotics [oral, intramuscular (IM), or intravenous (IV)] whereas smaller numbers of others received no antibiotics. For exploratory analyses, patients were divided into 4 subgroups based on the treatment chosen by their private physician: none, oral, IM, IV.

Because the treatment was chosen by numerous different private internists, the treatments varied greatly both in the actual choice of antibiotic, the duration of treatment during the interval, and whether or not different routes of antibiotics were used simultaneously or sequentially (eg, oral and IM, oral and IV). The only constant was that patients on IM antibiotics were all given penicillin G (benzathine penicillin G) for the first time. The majority of patients on oral antibiotics alone during the assessment interval were maintained on the antibiotics that they had been on prior to study entry. To be included in the oral, IM, or IV antibiotic groups, patients had to have received at least 10 days of treatment during the interim.

Statistics

Statistical tests included paired sample *t*-tests, analyses of variance (ANOVA), Tukey's HSD, Pearson Correlation, and analyses of covariance (ANCOVA) to control for baseline differences. Significance was defined as a two-tailed *P*-value of less than or equal to .05.

RESULTS

Description of Sample

There were 23 patients enrolled. Mean age was 42.7 years (SD 13.25), ranging from 20-65 years with a gender distribution of 30% male and 70% female. The mean length of time since diagnosis was 21.33 months (SD 22.2), ranging from 2 to 168 months. The symptom history of these 23 patients since the onset of Lyme disease included the following: memory loss (100%), arthralgias (96%), word-finding problems (91%), headaches (91%), excessive fatigue (87%), sleep disturbance (87%), irritability and mood lability (87%), arthritis (52%), recalled tick bite (39%), erythema migrans (total: 39% of which 26% were physician-diagnosed at the time and 13% were considered retrospectively by physicians to have been erythema migrans based on description), and Bell's palsy (13%). Of the 23 patients, 22 had had a reactive ELISA or Western blot for Lyme disease. The one historically seronegative patient had a clinical history of a physician diagnosed erythema migrans, arthritis, and Bell's palsy; this patient's serum was reactive on IgM Western blot from BBI Clinical Laboratories.

Study laboratory results on 19 patients were as follows. ELISA: IgG—1/19 reactive, 11/19 equivocal; IgM—0/19 reactive, 2/19 equivocal. Western blot: IgG—0/19 reactive, 5/19 equivocal; IgM—4/19 reactive, 7/19 equivocal. In 5 of 19 patients either a reactive ELISA or Western blot was found.

Assays for *B burgdorferi*-specific immune complexes were conducted on 16 patients. IgG *B burgdorferi*-immune complexes—8/16 reactive. IgM *B burgdorferi*-immune complexes—3/16 reactive. Neither IgG nor IgM *B burgdorferi*-immune complexes was found in 9 of 16 patients.

The mean duration of prior antibiotic treatment is shown in Table 1. An ANOVA failed to find a difference between the subgroups on the extent of prior oral antibiotics and prior IV antibiotics.

Time 1 (Baseline) Scores

Cognition. At baseline, the 23 patients as a group had average verbal, performance, and full scale IQ. However, these patients, as a group, had significant impairments in verbal memory, general memory, and delayed memory on the Wechsler Memory Scale when compared with the WAIS Verbal IQ and Full Scale IQ. When the 23 patients were subdivided into the 4 treatment groups and the baseline results on specific cognitive tests were compared using an ANOVA, no significant differences were found. Similarly, when comparison was made using a Tukey HSD analysis of multiple comparisons, no significant differences were found on the cognitive tests. In addition, at baseline, there were no statistically significant differences between the 4 treatment subgroups on the mean composite z score (oral 1.1±7.7; IV -3.6±22.6, IM 4.2±5.3; none -4.9±7.2).

Anxiety/Depression. On the Beck Depression Inventory, the 23 Lyme patients had a mean score of

Table 2. Percentage of time on antibiotics between Time 1 and Time 2 for 23 patients with chronic Lyme disease.

	Oral Group	IV Group	IM Group	No Antibiotic	All Groups
% of time on oral antibiotics	78.0±29.6	46.1±43.1	0	0	49.7±44.0
% of time on IV antibiotics	0	56.0±29.7	0	0	17.0±30.6
% of time on IM antibiotics	0	0	77.0±27.5	0	13.7±31.4
% of time on any antibiotics	78.0±29.6	67.2±26.9	90.8±18.5	0	59.9±39.9

Note. There were no significant differences among the antibiotically treated patients in either the percentage of time on any antibiotic or in the percentage of time on oral antibiotic during the interim.
Abbreviations: IM = intramuscular; IV = intravenous.

16.0±10.02 (range 2-43) indicating a mild level of depression for the group. On the Zung Anxiety Index, the mean score was 53.5±9.18, indicating a moderate level of anxiety for the group (range 41-74). There were no treatment subgroup differences on these two measures on a group ANOVA. No significant correlation was noted between the anxiety/depression scores and the degree of cognitive impairment at baseline. Anxiety and depression, however, were positively correlated (r = .647, *P* = .001).

Functional status. The scores on the subtests of the MOS-SF 36 Disability measure revealed marked disability among these patients with CLD: energy/fatigue 23.6±17.9, pain 35.8±24.7; emotional well-being 51.1±23.5, general health 39.4±24.2; physical functioning 49.1±21.5; role (physical) 13.6±25.3, role (emotional) 39.4±44.4; social functioning 40.3±31.1. There was no significant group difference among the 4 treatment subgroups on emotional well being, general health, physical functioning, role (emotional), role (physical), or social functioning. However, the groups were significantly different on energy/fatigue, with the least energy being reported by the patients who were subsequently given a course of IV antibiotic treatment (IV 9.2±5.6; IM 31.6±29 2, oral 22.9±11.6; none 37.0±18.6, F = 3.2, *P* = .048).

Treatment. During the four-month interval between assessments, 5 of the patients were given no treatment, 7 were given oral antibiotics only, 7 were given IV antibiotics (with or without oral antibiotics), and 4 were given IM antibiotics (with or without oral antibiotics). For the patients on one or more oral treatments only, these antibiotics included doxycycline, minocycline, amoxacillin, penicillin, azithromycin, clarithromycin, cefuroxime, and cefixime. The IM antibiotic used was benzathine penicillin G. Intravenous antibiotics included imipenem, cefotaxime, ceftriaxone, and vancomycin. Table 2 specifies the percentage of time between Time 1 and Time 2 the patients in each group were given antibiotics. No significant difference was noted between the groups of antibiotically-treated patients on the number of weeks treated between Time 1 and Time 2.

Time 2 Scores

Cognitive Change

A) Overall cognitive change. For the 18 antibiotically treated patients, the composite z score between Time 1 and Time 2 improved 6.1 standard deviations (*t* = 2.8, *P* = .012) compared with an improvement of only 2.8 standard deviations among the 5 patients who received no treatment (ANCOVA Any Abx v None, F = 4.9, *P* = .039).

B) Overall cognitive change by type of treatment. When the 23 patients were sorted into subgroups based on treatment received during the interim and their Time 2 scores were compared (controlling for baseline z-score differences), patients retreated with IV antibiotics did the best: the composite z-score improved 11.8 SD (median 8.9) for the 7 IV patients, 2.4 SD (median 2.5) for the 6 IM patients, 2.3 SD (median 2.0) for the 7 po patients (ANCOVA IV v PO, F = 6.9, *P* =.023), and 2.8 SD (median 2.0) for the 5 no antibiotic patients (ANCOVA IV v None, F = 10.58, *P* = .010).

C) Overall cognitive change and duration of treatment. There was no significant correlation between duration of time on antibiotics and composite z-score improvement. However, when the sample was divided into three groups based on the percentage of time on antibiotics between Time 1 and Time 2 (No Abx; Abx 50% of the time or less; Abx >50% of the time), the composite z-score improvement was 2.8 SD, 4.9 SD, and 6.5 SD respectively, suggesting that longer term treatment may be beneficial.

D) Neuropsychological subtest improvement. Comparing Time 1 and Time 2 using a paired samples *t*-test for the 18 antibiotically treated patients, marked improvement was noted in a variety of subtests including full scale IQ, performance IQ, verbal memory, general memory, attention/concentration, and delayed memory (Figure; Table 3). To examine whether memory within individuals improved over the four-month period, the dif-

Table 3. Baseline and time 2 scores for antibiotically treated patients (n=18).

Test	Time 1 (SD)	Time 2 (SD)	*t*-score	Df	*P*
Wechsler Adult Intelligence Scale-Revised					
Full scale IQ	102.2±16.6	109.1±11.9	-3.28	17	.004
Verbal IQ	102.7±16.2	106.2±9.1	-1.46	17	NS
Performance IQ	101.7±16.2	110.8±14.6	-4.60	17	<.001
Information	10.7±3.1	10.9±2.2	-.704	17	NS
Digit span	10.6±3.3	11.3±2.5	-1.42	17	NS
Vocabulary	11.0±3.3	11.3±2.2	-.56	17	NS
Arithmetic	10.6±3.4	11.2±2.2	-.871	17	NS
Comprehension	9.5±2.8	11.1±1.8	-3.12	17	.006
Similarities	10.3±2.8	10.6±1.6	-.615	17	NS
Picture completion	10.2±3.6	11.4±2.8	-1.64	17	NS
Picture arrangement	10.9±3.5	11.7±2.9	-1.04	17	NS
Block design	10.1±3.3	10.9±2.8	-1.6	17	NS
Object assembly	9.9±2.9	11.2±2.4	-2.36	17	.031
Digit symbol	10.1±3.1	11.1±3.0	-2.47	17	.028
Wechsler Memory Scale-Revised					
Verbal memory	92.9±19.1	102.3±14.9	-3.09	17	.007
Visual memory	104.1±19.5	110.4±12.7	-1.50	17	NS
General memory	95.1±16.7	106.6±14.9	-4.57	17	<.001
Attention/concentration	101.3±17.9	108.4±12.6	-1.96	17	.066
Delayed memory	94.9±16.9	109.9±15.8	-4.14	17	.001
Verbal fluency (FAS)	42.2±17.2	45.4±15.9	-1.03	17	NS
Beck Depression Inventory (n=17)	14.5±7.5	12.1±8.0	.863	16	NS
Zung Anxiety Scale	52.8±8.0	46.3±9.8	2.48	17	.024

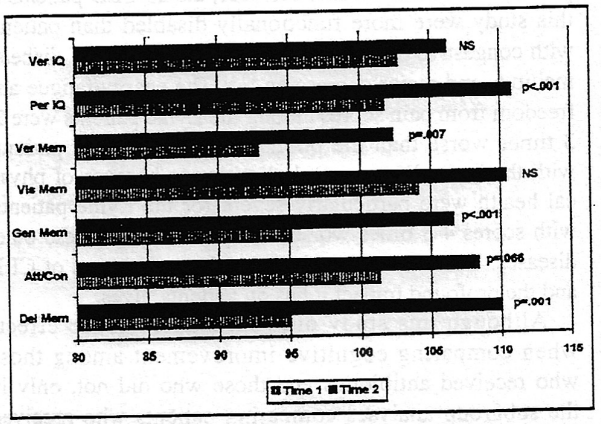

Figure. Change in cognitive scores for 18 antibiotically treated chronic Lyme disease patients.

ference between general memory and verbal IQ was calculated for each patient. The 18 patients given antibiotics significantly improved (narrowing the distance between general memory and verbal IQ by 4.6 scaled points) over the four-month interval whereas the 5 patients given no antibiotics worsened (broadening the distance between the two scores by 7.6 scaled points) (ANCOVA F = 5.22, *P* = .033).

E) Cognitive change associated with treatment received. When an ANCOVA was used to compare the Time 2 scores of the patients based on the treatment received during the interim, the IV group generally performed better than patients in the other groups. Significantly greater improvement was noted for the IV group compared with the oral group on the subtests of attention/concentration (F = 13.2, *P* = .005), general memory (F = 5.9, *P* = .038) and visual memory (F = 8. 1, *P* = .019). Marked improvement was also seen among the IV patients on verbal fluency and verbal memory. When the IV group was compared to the oral group, greater improvement was noted for the IV group on the subtests of attention/concentration (F = 4.2, *P* = .064), general memory (F = 5.3, *P* = .042), and visual memory (F = 27.1, *P* <.001).

F) Cognitive change associated with current laboratory seropositivity. No significant difference in mean improvement in cognition (composite z-score) was noted comparing antibiotically treated patients who did and who did not have currently reactive *B burgdorferi*-specific antibody levels using the criteria of either BBI Clinical Laboratories (ELISA or Western blot) or Dr. Coyle's Immune Complex assay. When we separated patients into two groups based on whether or not they met the two-tiered testing requirement of a reactive or equivocal ELISA and a reactive Western blot historically, no significant differences in mean improvement in cognition were noted.

Anxiety/Depression.

A) Overall change in depression/anxiety. Mild improvement on the Zung Anxiety scale and Beck Depression Inventory was noted among all 23 patients between Time 1 and Time 2. Significant improvement on the "Emotional Well-being" and "Role-Emotional" subtests of the MOS-SF 36 Rand functional status measure was noted among the 23 patients as a whole.

B) Overall psychiatric change by type of treatment. When the change in scores on anxiety and depression for the antibiotically treated patients between Time 1 and Time 2 were examined, a significant improvement was noted on the anxiety scale using a paired sample *t*-test. (Table 3). However, when an ANCOVA was used comparing Time 2 scores (controlling for Time 1 scores), no significant differences in anxiety or depression scores were noted based on presence or absence of antibiotic therapy or on route of treatment. Neither were significant changes noted between the individual subgroups on the scales of emotional well being and role functioning attributed to emotional health.

C) Correlation between psychiatric improvement and cognitive change. The percentage improvement in anxiety (10.7±19.4) was not correlated with improvement in cognitive z-score (5.36±8.22) among all 23 patients ($r = .415$, $P = .044$). Nor was there a significant correlation between percentage change in depression and improvement in cognition. Improvement in anxiety was, however, significantly correlated with improvement in depression ($r = .459$, $P = .032$).

Functional Status Improvement

A) Overall change in functional status. On the MOS-36SF for the antibiotically treated patients comparing Time 2 and Time 1, significant improvement was noted in the domains of energy/fatigue ($t = 2.4$, $P = .030$), pain ($t = 3.6$, $P = .003$), physical functioning ($t = 2.4$, $P = .028$), role physical ($t = 2.1$, $P = .048$), and social functioning ($t = 3.2$, $P = .005$). However, no significant differences were noted when an ANCOVA was used to compare the Time 2 scores of the patients who received no antibiotics and the patients who received any antibiotic, indicating that both groups showed functional improvement.

B) Overall functional change by type of treatment. A significant difference was not found using an ANCOVA when the functional status improvement of each of the 4 groups were examined together. However, when the patients who received IV antibiotics were compared with the other 3 groups (IM, oral, and no treatment) as a whole, there was greater improvement, even when baseline differences are controlled for, among the IV-treated patients in the areas of pain ($F = 3.0$, $P = .099$), energy/fatigue ($F = 6.2$, $P = .020$), general health ($F = 3.9$, $P = .063$), physical functioning ($F = 6.8$, $P = .017$), role physical ($F = 4.5$, $P = .047$), social functioning ($F = 5.0$, $P = .037$), and emotional well-being ($F = 5.4$, $P = .031$).

DISCUSSION

This study suggests that repeated courses of antibiotic treatment may result in objectively quantifiable cognitive improvement over a four-month interval among a group of patients each of whom had received more than the standard recommended course of antibiotic therapy previously. Further, the study suggests that for patients with Lyme encephalopathy the IV route of delivery may be most effective, not only in producing dramatic cognitive improvement but also by enhancing energy and decreasing pain, resulting in better physical, social, and emotional functioning. These results are consistent with the observations of physicians who note that many patients with persistent symptoms appear to benefit from repeated courses of antibiotic therapy, a phenomenon supportive of the persistent infection hypothesis.

Based on comparison with published data using the same functional disability measure (Short-Form 36) among patients with other chronic diseases, the 23 CLD patients in this study were more functionally disabled than patients with congestive heart failure, hypertension, type 1 diabetes mellitus, and major depression.[40,41] The energy/fatigue and freedom from pain scores among the Lyme patients were 2-3 times worse than the published scores among patients with the latter diseases. Role limitations because of physical health were particularly severe for the Lyme patients, with scores 4-8 times worse than patients with these other diseases. These results underscore the seriousness of CLD and the profound impact it has on patients' lives.

Although this study did find marked group effects when comparing cognitive improvement among those who received antibiotics and those who did not, only in the subgroup analyses comparing patients who received IV antibiotics to all others did we find significant differences on the functional disability measures. This suggests that IV antibiotics may be particularly effective and that neuropsychological tests may be a more sensitive measure of change over time than self-report disability measures. Studies of patients with encephalopathy that rely on the

MOS-36SF as a major outcome measure may need much larger sample sizes and longer durations of follow-up to show differences between treated and untreated samples.

The majority of the patients in this study were not depressed. The group anxiety level was moderate in intensity. No significant relationship was found between amount of depression and anxiety at baseline and overall cognitive impairment. Nor did we find that the more depressed patients at baseline had the least amount of cognitive dysfunction, as had been found in an earlier study of patients with CLD.[42] Contrary to the hypothesis that attributes many of the symptoms of CLD to somatization, anxiety and/or depression (ie, a psychogenic hypothesis)[43] the majority of patients with CLD in our study were not suffering from significant levels of psychopathology. Further, patients who were more depressed or anxious were just as likely to respond to antibiotic therapy with an improvement in cognition as those who were less depressed or anxious.

Several factors need to be addressed regarding the limitations and strengths of this study. First, because we employed the same battery of neuropsychological tests separated by only four months, a repeated testing (practice) effect that artificially improved the Time 2 scores most likely occurred. A repeated testing effect, however, could not alone account for the marked improvement among the antibiotically-treated patients because comparable improvement was not noted among the 5 patients who received no treatment but who also were retested. The fact that the pattern of improvement sorted out differently for the treatments (IV > other or none) suggests that there was in fact improvement that could be attributed to the specific route of antibiotic delivery. This improvement might relate to the better CNS penetration provided by the IV route or to the drama of an invasive procedure. If the latter were true, one might expect that the patients who received IM injections would have shown greater improvement than the patients who received oral or no treatment because the IM group also was receiving a new and invasive treatment. This was not the case. Although we doubt that the drama of IV therapy alone could account for the marked cognitive and functional improvement noted in our small sample, only a placebo-controlled IV therapy study could prove this for certain.

Second, because of our small sample size, statistically significant differences between treatment groups at Time 1 and Time 2 would be hard to detect. The fact that significant differences did emerge from the Time 2 treatment subgroup analysis is surprising. However, definitive conclusions about the benefit of a specific route of antibiotic therapy cannot be made because the treatment selection was neither uniform nor randomly assigned. Further confounding the conclusions about the relative benefit of one route of treatment versus another is that many patients received two antibiotics simultaneously (ie, oral and IV, oral and IM). The results of our study may suggest to the reader that oral antibiotic therapy is ineffective for patients with chronic Lyme encephalopathy because the improvement in cognition among the patients on oral antibiotics alone was no better than among the patients who received no antibiotic therapy. We feel that this conclusion is unwarranted because the patients who had been on oral antibiotics and whose physician did not choose to switch to another route or add another route of antibiotic delivery tended to continue on that same oral antibiotic. In other words, whereas the patients given IV or IM antibiotics were all starting either a new therapy or one that they had not received for many months, the patients on oral antibiotics alone were merely being maintained on an ongoing treatment. However, the study does suggest that there may be a particular benefit to a repeated course of IV antibiotic therapy once response has leveled off.

Third, is it possible that fatigue accounted for the poor cognitive performance among the IV-treated patients at baseline and that a resolution of their systemic fatigue could account for much of the cognitive improvement? Krupp et al[42] observed that fatigue was highly correlated with poor cognitive performance in a sample of patients with persistent Lyme encephalopathy. In our sample, although there were no statistically significant cognitive differences at baseline that distinguished the different groups, there was a difference in the level of fatigue among the different treatment groups: patients selected for IV antibiotics suffered the greatest fatigue; patients given oral or IM antibiotics had moderate levels of fatigue; and patients given no antibiotics had the least amount of fatigue. If fatigue is a marker of greater illness severity, then the IV group appears to have been sickest. Based on simple regression to the mean, their energy levels would have been the most likely to improve, perhaps contributing to the improvement in their cognitive scores. In fact, when baseline level of fatigue is used as a covariate, no significant difference is noted between the treatment groups on the overall degree of cognitive improvement. In other words, improvement in energy and cognition run together. One possible explanation for these results relates to a decrease in fatigue and cognitive disturbance because of a decrease in inflammatory cytokine production that had been triggered by persistent peripheral or central infection. Although regression to the mean in fatigue level might have contributed to some of the cognitive improvement, we doubt that regression to the mean alone could by itself account for the robust improvement in cognition seen among the patients given antibiotics in general (6.1 SD) and IV antibiotics in particular (11.8 SD), particularly when

one considers that the patients who received no antibiotics had the lowest mean cognitive z-score at baseline and their improvement was far more modest (2.8 SD).

Fourth, because of the time our study was designed, the laboratory criteria for inclusion made use of the pre-1994 CDC criteria of either a reactive ELISA or Western blot. The current CDC guidelines recommend two-tiered testing: an equivocal or a reactive ELISA is to be followed by a Western blot assay.[37] If we examine our data comparing the historical laboratory results of patients who would be considered seropositive by this two-tiered method with patients whose results did not meet this two-tiered standard (using the more inclusive, varied, and less standardized Western blot criteria employed by the individual laboratories conducting the tests at that time), there is no difference in the cognitive change score between the two antibiotically-treated groups. In other words, the two-tiered method of laboratory testing did not help to identify patients who were more or less likely to respond to antibiotic therapy. Further, it should be noted that only 4 of the 19 serum samples were Westem blot reactive, and each of these was a reactive IgM not an IgG Western blot. Of these 7 patients who received a repeated course of IV antibiotics, none had a reactive Western blot. Had these patients been denied treatment based on not having a currently positive Western blot result, these patients most likely would not have improved.

Fifth, because this was a small uncontrolled pilot study that did not have randomly assigned and blinded treatment assignment, no definitive conclusions can be drawn from this study. For example, the study results may have been adversely effected or skewed by the small numbers of patients, by the lack of a blinded IV placebo treatment, and by the fact that nonrandom treatment assignment raises the likelihood that extraneous confounding factors were present but not identified by us.

In summary, our pilot study suggests that repeated courses of antibiotic therapy, in particular when given intravenously, can be effective for patients with a history of Lyme disease who have persistent cognitive problems despite robust prior treatment. In addition, our study suggests that currently "seronegative" patients may be just as likely to respond to treatment as currently "seropositive" patients. These "suggestive" findings need to be tested by a placebo-controlled study using a larger sample size, randomized and uniform treatment assignment, blinded evaluators, and separate randomization of patients who meet the CDC's current laboratory criteria for the diagnosis of Lyme disease and those who don't.

ACKNOWLEDGMENT

The authors wish to thank Patricia Coyle, MD, for conducting the immune complex assays. Partial funding support for this study was provided by the Lyme Disease Association of New Jersey and a NYS Psychiatric Institute Research Support Grant.

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