Journal of Spirochetal and Tick-borne Diseases

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Letter to the Editor*

The archy of Triumph?

Excerpts from "archy declares war" by the famous *New York Sun* columnist, archy the cockroach, as they appeared overnight on the typewriter of Don Marquis, newspaper reporter:

i am going to start
a revolution...
i shall organize the insects...
hearken to my calling...
black legged spiders
with red hearts of hell...
come, come, come...
bloodsuckers wriggle
out of the bayous
ticks cooties hornets...
this is war
...you are strong...
come in your billions
tiny small feet...
man is at your mercy
one sudden gesture
and all his empires perish
rise...

If it sounded like that was a call-to-arms between bloodsuckers and humans circa 1916 when the above column was written, the Star Wars of conflicts between species today is that of ticks and mankind, and the deer ticks are gaining.

There was an increase in reported cases of Lyme disease last year in our own aptly named Bucks County, Pennsylvania, but that tally represented just the tip of the iceberg. A Centers for Disease Control and Prevention study revealed that there has been, overall, at least a 30 times increase in reports of Lyme disease cases over the past 12 years. Other agencies indicated the total number of cases may be in the range of 1 to 2 million in the United States—many unrecorded by official agencies.

Tick-borne diseases, including many common pathogens—bacteria, viruses, parasites, and the spirochete that causes Lyme disease—are taking over our favorite places. The plain truth is that it is really not safe to live an outdoor life normally. The "archies" of the tick world are equal-opportunity warriors and have been known to deck muscled Marines as easily as bird watchers or other innocent civilians.

The great out-of-doors, beloved by most well-adjusted people, has become enemy turf and has to be retaken. The fields, yards, woods, parks, mountains, resorts, and riversides we know and love, all are landmined with the vectors of human misery and yes, sometimes death. The fact that more than 1/2 of the nearly-invisible ticks out there are infected with these human pathogens seldom makes the news.

No one wants to cause undue alarm; no one wants to lower real estate values or cause resorts to lose income. Therefore, very little is said in warning about the teeming hordes lying in ambush. While we medics are oriented to the prevention of individual suffering, in military terms there is an even more important strategy—serious enemies must be "terminated with extreme malice." The choice of weapons is important. Unless archy's vision of success via the very magnitude of his "billions" is anticipated by our generals, efforts will continue to be diverted away from the need to develop antitick grenades, not just spirochete-seeking missiles, as important as those are.

Archy was prescient—the confrontation between species could be won, he thought, if the multilegged critter forces joined in an effort of great magnitude. . .they have. Tick-borne diseases are allied coinfectors. If we do not want a generation of physically and mentally weakened Americans who are chronically ill with Lyme disease, babesiosis, ehrlichiosis, and other increasingly local, no longer exotic, tick-carried pestilences, we need a new battle plan. The campaign into which we are heading will have to be restrategized to eliminate ticks.

Militarily speaking, we might be able to terminate the principal tick hosts such as deer and mice if we could get medicine's Joint Chiefs of Staff to acknowledge the enormity of this plague. Currently, that aspect is being ignored by their high command in academia, Washington, and the Centers for Disease Control and Prevention. This is war! Right, archy?

Virginia T. Sherr, MD
Holland, Pennsylvania

**Virginia T. Sherr, MD, is a physician from Holland, Pennsylvania, whose concern about the effects of Lyme disease and other tick-borne infections has inspired her journalistic crusade.—The Advance of Bucks County, PA.*

The Spectrum of Gastrointestinal Manifestations in Children and Adolescents with Lyme Disease

Martin D. Fried, MD; Matthew Abel, MD*; Dorothy Pietrucha, MD†; Yen-Hong Kuo, MS‡; and Aswine Bal, MD§*

ABSTRACT

A clinical diagnosis of Lyme disease was made in 15 consecutive patients between the ages of 8 and 20 years who presented with a history of an erythema migrans rash followed by chronic gastrointestinal symptoms and multiple organ system complaints. Endoscopic evaluation was performed to assess the gastrointestinal mucosa and to obtain biopsies for polymerase chain reaction (PCR) to the outer surface protein A (Osp A) of *Borrelia burgdorferi*. As age matched controls, 10 patients with biopsy-proven Crohn's disease were also tested by PCR. The laboratories assessing the histopathology and performing the PCR were blinded to the diagnosis of all specimens.

The presence of *B burgdorferi* DNA in the gastrointestinal tract was confirmed by PCR in all of the patients with the clinical diagnosis of Lyme disease who had chronic gastrointestinal symptoms and in two control subjects with Crohn's disease. Biopsy evidence of chronic gastritis, chronic duodenitis, and chronic colitis was found in patients with Lyme disease who had chronic gastrointestinal symptoms and was associated with the presence of *B burgdorferi*.

The chronic gastrointestinal symptoms that occurred within 6 months of an erythema migrans rash and Lyme disease may be attributed to a direct effect or immune mediated response to *B burgdorferi*.

Key words: Lyme disease, abdominal pain, blood in stool, *Borrelia burgdorferi*, gastritis, duodenitis, colitis, polymerase chain reaction

INTRODUCTION

Lyme disease affects a wide range of organ systems, producing dermatologic, musculoskeletal, neurologic, genitourinary, lymphatic, hepatic, renal, respiratory, cardiovascular, and ocular manifestations.[1,2] One report to date describes the presence of *Borrelia burgdorferi* in the stomach, intestines, and colon of children.[3] To further address the clinical manifestations of Lyme disease and the possibility of direct involvement of the gastrointestinal (GI) tract, a prospective study was made of 15 consecutive patients who had a physician documented erythema migrans (EM) rash followed by chronic gastrointestinal symptoms and multiple organ system complaints of Lyme disease.

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METHODS

All patients included in our study had a physician documented EM rash with no prior history of gastrointestinal complaints. They were referred to the pediatric gastroenterology and nutrition service of Jersey Shore Medical Center for evaluation of chronic abdominal pain, chronic diarrhea, acid reflux, or blood in the stool that occurred within 6 months after the onset of the EM rash. From January 1998 through April 1999, 15 consecutive patients satisfying the above clinical criteria[4] were evaluated prospectively. There were 6 boys and 9 girls evaluated (mean age 14±3.6 years, range 8-20). Each case included a history, physical examination, complete blood cell count, liver function tests, sedimentation rate, antinuclear antigen (ANA), HLA B27, esophagogastroduodenoscopy (EGD), and/or colonoscopy. A Lyme Western blot was performed

for confirmation of an acute (immunoglobulin M) or past (immunoglobulin G) *B burgdorferi* infection. A positive IgM Western blot was interpreted as 2 of 3 bands (23, 39, 41 kd). A positive IgG Western blot was interpreted as 5 or more of the following *B burgdorferi*-specific bands: 18, 23, 28, 31, 34, 39, 41, 45, 58, 66, 93 kd. A diet history was taken to assess the dietary fat intake. Ultrasonography of the abdomen was performed when the history suggested a diagnosis of gallstones or pancreatitis. Stool samples were examined for occult blood, *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, ova and parasites, and *Clostridium difficile* toxin. Gastrointestinal (GI) biopsies were reviewed to assess the mucosa by microscopy and whether *Helicobacter pylori* (on EGD only) or eosinophilia was present.

Biopsy specimens were taken from areas of the GI tract that looked inflamed during EGD or colonoscopy. The biopsies were assigned randomly to three histopathologists who were blinded to the diagnosis of the specimens they received. The histopathologists did not perform a silver stain for the detection of spirochetes because it is not routinely done. Biopsies were reported as acutely inflamed when polymorphonuclear cells were present in the mucosa and chronically inflamed if 6 or more plasma cells and lymphocytes were present in the gastric mucosa without polymorphonuclear cells. Chronic duodenitis or chronic colitis was diagnosed when more than 6 intraepithelial lymphocytes per 100 surface absorptive cells were present in tissue biopsies in conjunction with a distortion in glandular architecture.

Polymerase chain reaction (PCR) for DNA to *B burgdorferi*[5] was performed on all biopsies by Medical Diagnostic Laboratories in Mount Laurel, New Jersey. In all patients in which *B burgdorferi* DNA was detected, PCR for *B burgdorferi* RNA polymerase was performed and results are reported in the Table. As a target for DNA amplification, the gene coding for the outer surface protein A (OspA) of *B burgdorferi* was selected and analyzed as described below.

DNA Isolation from Biopsy Specimens

Total DNA was extracted from duodenal, gastric, and colonic biopsies as described by Maniaties et al.[6] The samples were centrifuged (5 minutes, 4°C, 14K rpm) and the pelleted biopsy was subjected to 500 µL of cell lysis buffer [0.5% SDS, 470 µL TE buffer, 5 µL of proteinase K (20 µg/µL)]. The samples were incubated for 24 hours at 50°C. Proteinase K (5 µL) was added to the mixture every 6 hours. DNA was extracted by phenol chloroform, followed by ethanol precipitation. DNA concentrations were determined spectrophotometrically by measuring the A_{260}.

DNA Amplification

The SL primers (SLA 5′-AAT AGG TCT AAT AAT AGC CTT AAT AGC-3′ SLB 5′ CTA GTG TTT TGC CAT CTT CTT TGA AAA-3′) are suitable for amplification of all *B burgdorferi* sensu lato isolates. The SL primers amplify a region (nucleotide 21-328) of the *B burgdorferi* senso stricto B31 OspA sequence. One µg of isolated DNA was used as a template DNA in the presence of a 20 pmol sample of each primer in a 50 µL reaction mixture. The samples were subjected to 35 amplification cycles in a Perkin Elmer 2400 thermocycler (Foster City, CA) under the following conditions: 93°C, 1 minute; 65°C, 1 minute; and 72°C, 1 minute. PCR amplification products were resolved onto 1.5% agarose electrophoresis gels and visualized under ultraviolet light with ethidium bromide.

To test the presence of inhibitory substances and to provide a positive control in the PCR assay, amplifications were also performed with primers targeting the histone gene. A positive control was performed with every biopsy specimen. It included a PCR in the presence of 100% *B burgdorferi* DNA that was purchased from the American Type Culture Collection (Rockville, MD). This *B burgdorferi* DNA was isolated from *Ixodes scapularis* tick, New York Type strain, and shipped frozen to the laboratory.[7] The negative control performed with each biopsy specimen included the PCR in the absence of DNA. A second genomic DNA control is done weekly at the laboratory as part of their quality control. Physical containment measures ensured the absence of DNA contamination in the PCR procedure.

As age-matched controls, 10 adolescents with biopsy proven Crohn's disease (5 boys, 5 girls, 13.5±2.5 years, range 10-17), who had not been on antibiotics one year prior to endoscopy, were also tested by PCR. The laboratory performing the PCR analysis was blinded to the diagnosis of all specimens they received.

Statistical Analysis

The sensitivity and specificity of PCR for the detection of *B burgdorferi* in the GI tract was calculated. The confidence intervals (CI) were calculated by using the Fischer's Exact test method. A Fischer's exact test was used to determine the association between inflammation and PCR positivity in each of the biopsied sites.

RESULTS

Patients with Lyme disease presented with chronic abdominal pain (n=10, 67%), chronic diarrhea (n=1, 7%), visibly evident blood in the stool (n=2, 13%), and acid reflux with heartburn (n=2, 13%). In all 4 patients whose biopsies revealed evidence of colitis, the abdominal pain was characterized as a crampy, periumbilical pain that started at the right middle quadrant of the abdomen and spread to the left middle quadrant of the abdomen or vice versa. The pain was unrelated to meals and occurred

Table. The gastrointestinal manifestations and biopsy results of patients with Lyme (1-15) and Crohn's disease (A-J).

Patient	Antibiotics (months)*	Chief complaint	Gastric biopsy	Duodenal biopsy	Colon biopsy	Gastric PCR†	Duodenal PCR	Colon PCR
1	5	abdominal pain	gastritis	duodenitis	colitis	DNA	DNA	DNA/RNA
2	4	blood in stool	gastritis	(-)	colitis	DNA	(-)	DNA
3	4	acid reflux	(-)‡	(-)	NB	DNA	(-)	NB
4	3	abdominal pain	gastritis	(-)	(-)	DNA	DNA	(-)
5	5	abdominal pain	gastritis	duodenitis	(-)	(-)	DNA	(-)
6	5	abdominal pain	(-)	(-)	NB	DNA/RNA	(-)	NB
7	2	diarrhea	(-)	(-)	colitis	DNA	(-)	DNA
8	0	abdominal pain	gastritis	(-)	(-)	(-)	(-)	DNA/RNA
9	2	abdominal pain	gastritis	(-)	(-)	(-)	(-)	DNA/RNA
10	0	abdominal pain	gastritis	(-)	NB	DNA	(-)	NB
11	0	blood in stool	NB§	NB	colitis	NB	NB	DNA/RNA
12	1	abdominal pain	gastritis	duodenitis	NB	(-)	DNA	NB
13	2	abdominal pain	(-)	(-)	NB	DNA	(-)	NB
14	0	abdominal pain	(-)	(-)	NB	(-)	DNA/RNA	NB
15	0	acid reflux	gastritis	(-)	NB	DNA	(-)	NB
A	0	blood in stool	(-)	(-)	granuloma	(-)	(-)	(-)
B	0	abdominal pain	(-)	(-)	granuloma	(-)	(-)	DNA
C	0	abdominal pain	gastritis	duodenitis	granuloma	(-)	(-)	(-)
D	0	abdominal pain	(-)	(-)	granuloma	(-)	(-)	(-)
E	0	abdominal pain	gastritis	duodenitis	granuloma	(-)	(-)	(-)
F	0	abdominal pain	granuloma	(-)	granuloma	(-)	(-)	(-)
G	0	blood in stool	NB	NB	granuloma	NB	NB	DNA
H	0	blood in stool	NB	NB	granuloma	NB	NB	(-)
I	0	abdominal pain	gastritis	duodenitis	granuloma	(-)	(-)	(-)
J	0	abdominal pain	(-)	(-)	granuloma	(-)	(-)	(-)

**Number of months of antibiotic treatment for Lyme disease prior to GI biopsy.*

†PCR-DNA denotes the detection of B burgdorferi *DNA (the outer surface protein A) by PCR of biopsy specimens. DNA/RNA denotes the detection of* B burgdorferi *DNA and RNA polymerase by PCR of biopsy specimens.*

‡(-) denotes no histological pathology detected on biopsy or no detection of B burgdorferi *by PCR.*

§NB denotes an area of the gastrointestinal tract that was not biopsied and a PCR test that was not performed due to the absence of a specimen from that site.

Abbreviations: DNA = deoxyribonucleic acid; NB = not biopsied; PCR = polymerase chain reaction; RNA = ribonucleic acid.

throughout the day. In the remaining 6 patients with abdominal pain whose biopsies revealed gastritis, duodenitis, or both, the abdominal pain was characterized as periumbilical, burning, and improved by avoiding fried foods and foods high in fat content. Ultrasonography of the abdomen did not reveal any gallstones or evidence of pancreatitis. In 2 patients who complained of acid reflux, their pain was a burning midepigastric pain that radiated to the esophagus. The pain occurred within the first postprandial hour and was relieved by antacids. Ten of the 15 patients with Lyme disease had evidence of inflammation at a biopsy site with detection of *B burgdorferi* DNA at that site. Patients 2 and 11 had blood in their stool and presented with the clinical features of Crohn's disease (ie, 15 pound weight loss in a year, arthritis of the knee, protein losing enteropathy) and ulcerative colitis (6 bloody bowel movements a day for a week), respectively. The biopsies of all the patients with Lyme disease revealed no evidence of granulomas or terminal ileitis. In patient 6, the IgM Western blot was positive and showed

the 23, 31, 34, 39, 41, 58, and 66 kd bands. The IgG Western blot was negative (no bands present). No other patient had a positive Western blot. All control patients with Crohn's disease had biopsy proven terminal ileitis and granulomatous colitis. Lyme disease was diagnosed in 15 patients and 2 with Crohn's disease had a positive PCR to *B burgdorferi* DNA in biopsy specimens from the gastrointestinal tract (Table). In 6 patients with Lyme disease, *B burgdorferi* DNA was detected in the GI tract and *B burgdorferi* RNA polymerase was detected by PCR.

A positive *B burgdorferi* PCR occurred with chronic inflammation in the GI tract of 11 of 15 patients with Lyme disease. In patients 8 and 9, inflammation occurred in the stomach; however, *B burgdorferi* DNA was detected in the colon. *B burgdorferi* DNA was detected in the GI tract in the absence of inflammation in 4 patients (27%), 3 of whom had received at least 2 months of antibiotics prior to endoscopy. There was no statistically significant association between PCR positivity in the GI tract and chronic inflammation.

In 10 of 15 patients (67%), antibiotic therapy for Lyme disease had been prescribed within 1 to 5 months prior to endoscopy (n=4, 1-2 months; n=3, 3-4 months, and n=3, 5 months). Despite prior antibiotic use, all 4 patients with colitis were PCR positive for *B burgdorferi* DNA in the colon while 5 of 9 with gastric inflammation were PCR positive in gastric biopsies. *Helicobacter pylori* was not detected in any of the gastric biopsies. *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, and *Clostridium difficile* toxin was not detected in any of the stool samples. HLA B27 was positive in patients 1 and 11 and in none of the controls. ANA was positive and had a speckled pattern in patients 2, 5, and 6. An elevated sedimentation rate of 85 and 28 were found in patients 4 and 13, respectively.

The lab performing the PCR had a false positive rate of 1 in 500 by analyzing 6550 specimens from January 1998 through April 1999. The sensitivity of GI *B burgdorferi* DNA detection was 100% (15/15) with a 95% CI (81.9%, 100%). The specificity was 80% (8/10) with a 95% CI (44.4%, 97.5%). The positive predictive value was 88.2% (15/17) with a 95% CI (63.6%, 98.5%).

DISCUSSION

Abdominal pain and the associated GI pathology in children with Lyme disease whose biopsies are PCR positive for *B burgdorferi* has not been reported previously. The presence of an EM rash in the past or a positive Western blot and chronic GI symptoms in the past does not mean that the two are related. However, positive detection of the OspA gene in biopsies confirmed the presence of *B burgdorferi* DNA in the biopsied tissue samples while offering the advantage of no cross reaction with other spirochete species that have been previously detected in the GI tract.[8-10] It is possible that PCR, a highly sensitive method, could lead to false positive results because of the amplification of similar sequences of related microorganisms. However, a false positive rate of 1 in 500 biopsy specimens suggests that this occurs infrequently.

B burgdorferi may contribute to GI symptoms by its presence directly in the GI tract or by eliciting an inflammatory or immune response.[11,12] In 11 patients (73%), inflammation in the GI tract was accompanied by a positive PCR to *B burgdorferi* suggesting an association between the infection and inflammation in these patients. In 2 patients the detection of the DNA occurred at a site distant from the inflammation. In the absence of inflammation, the presence of *B burgdorferi* may have contributed to abdominal pain and acid reflux (patients 3, 6, and 13).

Most available evidence suggests that appropriate antimicrobial treatment is highly efficacious to cure Lyme disease. As previously reported,[13,14] we found that *B burgdorferi* persisted even after 1 to 5 months of antibiotic therapy. Despite prior antibiotic therapy, we were still able to detect *B burgdorferi* DNA and RNA polymerase in these patients. The detection of RNA polymerase in 5 patients suggests that the infection was actively replicating. In two cases (patients 1 and 6), this active replication occurred despite 5 months of antibiotic therapy for Lyme disease. Previous work has demonstrated that *B burgdorferi* can invade human fibroblasts and be protected from antimicrobial action.[15] The ability of the organism to survive in this intracellular environment is one mechanism by which it may evade the immune response of the host and thus persist. Antibiotic resistance is another method that could explain the persistence of the organism despite prior antibiotic therapy. While the detection of *B burgdorferi* may represent evidence of prior or ongoing Lyme disease, it may not be the only etiology of the patients' abdominal symptoms.

Duray and Steere[16] reported that *B burgdorferi* elicits interleukin-1, collagenase, prostaglandin E2, and circulating immune complexes. Some of these immune complexes may exert their effect at a distant site from the infection. Two patients (8 and 9) illustrate this possibility. In each case, *B burgdorferi* was detected in the colon but the inflammation was found in the stomach.

An inflammatory or immune reaction as a result of Lyme disease could affect the colon and may persist because of circulating immune complexes.[16] Inflammatory and immune etiologies have also been proposed in Crohn's disease[17,18]; however, this is the first report to describe the detection of *B burgdorferi* in patients with Crohn's disease. The role of *B burgdorferi* in patients with Crohn's disease needs further investigation.

CONCLUSION

Children and adolescents with a history of Lyme disease and chronic GI symptoms occurring within 6 months of an EM rash, had evidence of inflammation in the stomach, duodenum, and colon. We found *B burgdorferi* by PCR of GI biopsies to be associated with chronic inflammation. The inflammatory reaction we describe may have been caused by spirochetes or by immune system products elicited in response to the spirochete presence.

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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

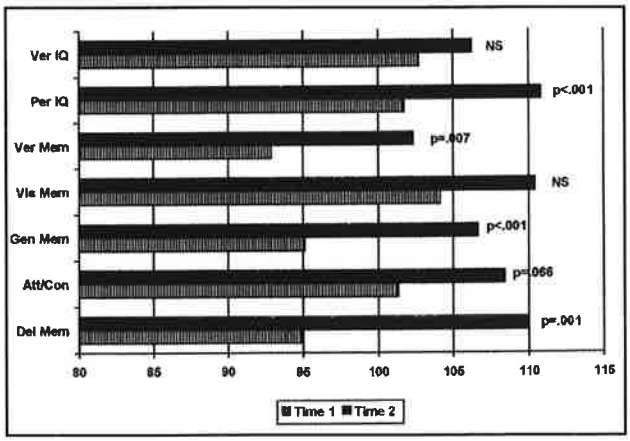

Figure. Change in cognitive scores for 18 antibiotically treated chronic Lyme disease patients.

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 Westem 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

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Antiphospholipid Antibody Syndrome and Lyme Disease: A Possible Association

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ABSTRACT

Antiphospholipid Antibody Syndrome (APS) and Lyme disease both result in affected patients having elevations in anticardiolipin antibodies (ACAS). The literature suggests that these antibodies lead to characteristic clinical findings in APS only, and have no clinical significance in Lyme disease. We present a patient who had symptoms suggestive of APS and elevated ACAS levels to support the diagnosis. Her antibody levels decreased upon treatment for Lyme disease, however, suggesting the symptoms were actually a result of a Lyme disease related elevation in her ACAS levels. The possible association between Lyme disease and APS warrants further research.

Key words: Lyme disease, Antiphospholipid Antibody Syndrome, anticardiolipin antibodies

Lyme disease is a multisystem infection caused by the spirochete *Borrelia burgdorferi*. Lipids on the surface of *B burgdorferi* may cross-react with IgM and IgG anticardiolipin antibodies (ACAS), causing elevations in the levels of one or both of these antibodies on ELISA screens.[1] Antiphospholipid Antibody Syndrome (APS), an autoimmune mediated disease that is distinct from Lyme disease in its clinical presentation, also results in the elevation of these ACAS. In APS, the elevated level of ACAS has been linked to its clinical manifestations, which include cerebrovascular changes, thrombotic events, and spontaneous and recurrent abortions.[2] To date, this has not been found to be the case when ACAS are high in patients with Lyme disease.[3] Herein, we report a case of a patient with a longstanding documented diagnosis of APS in whom both elevated ACAS as well as clinical evidence of the disease existed. The patient was later found to have Lyme disease and underwent treatment for it. Surprisingly, during her antibiotic therapy, her ACAS fell to within normal limits, suggesting that these levels were most likely elevated because of the presence of *B burgdorferi* antigens and thus not a result of APS. This being the case, it is also likely that her clinical symptoms, originally attributed to APS, are also a result of Lyme disease related elevations of ACAS.

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CASE REPORT

A 37-year-old white female was referred for treatment after she was found to have a positive Western blot, which met the Center for Disease Control and Prevention criteria for the diagnosis of Lyme disease. The patient reported the history of a successful pregnancy and delivery of a healthy child. A few years later two episodes of fetal wastage and miscarriages occurred, despite Heparin therapy during pregnancy. At that time, after testing positive for elevated levels of IgM and IgG ACAS, she was given the diagnosis of APS and referred to a hematologist for evaluation of the disease. Her hematologist tested her and found her to have Lyme disease.

Upon our questioning, the patient reported no recollection of a specific tick bite or erythema migrans rash and did not show clinical signs or symptoms of Lyme disease including joint pain, headaches, confusion, arthralgias,

myalgias, or disabling fatigue. She did, however, have many risk factors for its acquisition. She grew up in and now lives in areas endemic for Lyme disease and has family members in other areas endemic for the disease. Her husband works as a biologist in a nearby state park and has had as many as 100 deer ticks on him after coming home from work. He very likely could have acted as a vector for the transmission of the tick to the patient.

The physical examination revealed a very pleasant, healthy appearing woman. Her vital signs were stable and within normal limits. Her head, ears, eyes, nose, and throat examinations were normal. Her cranial nerves were intact and her neck was supple and without lymphadenopathy. The pulmonary examination was normal. On cardiac examination, normal S1 and S2 were heard without evidence of a gallop, murmur, or rub. Her abdominal exam was normal without organomegaly, masses, or tenderness. Her extremities were grossly normal. There was no evidence of synovitis or effusions, and her joints were mobile and without pain. Neurologic examination did not reveal any lateralization, and her cutaneous examination was normal.

A laboratory evaluation resulted in a normal complete blood count. The patient is blood type O and Rh negative. Her coagulation profile was normal. Our blood test found her antiphospholipid IgM levels to be positive at 13 MPL units and her Lyme ELISA IgM and IgG levels to be at an index of 1.33 and 1.37, respectively. She was Lupus anticoagulant negative, rheumatoid factor negative, micro somal antibody negative, and antinuclear antibody negative. Although her Lyme Western blot IgG was negative, her IgM Western blot was positive with bands noted at 66, 41, and 23 kd.

Based on the epidemiological risk factors and laboratory results, the diagnosis of infection with *B burgdorferi* was made. After declining intravenous antibiotic treatment the patient was started on intramuscular Bicillin injections at 1.2 million units IM every four weeks. Other than a severe Jarisch-Herxheimer reaction, the drug therapy was tolerated well. After four months of IM injections, the patient's anticardiolipin IgM fell to 7 MPL units, and after seven months of treatment, it was normal at 5 MPL units. The IgM antibody levels have remained negative.

DISCUSSION

The literature states that patients whose anticardiolipin antibody levels are elevated as a result of Lyme disease, rarely, if ever, present with clinical symptoms like those found in patients with APS elevated anticardiolipin antibody levels.[4] In our patient, given her history and presentation, this may not be the case. She had a healthy, full-term delivery followed by two miscarriages. These miscarriages were temporally associated with elevated ACAS. When the patient was later diagnosed with and treated for Lyme disease, her anticardiolipin antibody levels fell to within normal limits. Because of this, we believe if indeed her miscarriages were a result of her high ACAS, Lyme disease was the cause rather than APS. Furthermore, we propose that like our patient, other patients currently carrying the diagnosis of APS may instead be suffering from Lyme disease masquerading as APS. Further study should be done on the possible association between Lyme disease and the symptoms of APS. This could include the use of Lyme disease screening in diagnosed APS patients who live in areas endemic for Lyme disease, or the use of tests that distinguish autoimmune ACAS from nonautoimmune ACAS.[2,5]

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Rapid Susceptibility Testing of Lyme Disease Spirochetes by Flow Cytometry

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ABSTRACT

Flow cytometry has recently become an effective tool for rapidly determining antimicrobial susceptibilities of microorganisms pathogenic to humans. In this study, we developed an in vitro assay that used flow cytometry to detect rapidly (18 hours) the minimum bactericidal concentrations (MBC) of antimicrobial agents against several isolates of *Borrelia burgdorferi* sensu lato. Acridine orange fluorescence intensity and number of events were used to detect killed spirochetes incubated in Barbour-Stoenner-Kelly (BSK) medium containing decreasing concentrations of antimicrobial agents. The flow cytometric susceptibility assay accurately predicted MBC values for amoxicillin (0.06 µg/mL), cefotaxime (0.06 µg/mL), ceftriaxone (0.03 µg/mL), doxycycline (0.25 µg/mL), and erythromycin (0.13 µg/mL). In addition, the flow cytometric procedure rapidly detected significant variations in MBC values among *Borrelia* isolates. We conclude that flow cytometry is a rapid and accurate method for determining MBC values of antimicrobial agents against *B burgdorferi* sensu lato. Additionally, the use of flow cytometry will aid in the rapid evaluation of newly developed antimicrobial agents and provide a more accurate assessment of in vivo concentrations necessary to eliminate *B burgdorferi* sensu lato infections.

Key words: *Borrelia burgdorferi,* flow cytometry, susceptibility testing

INTRODUCTION

Lyme borreliosis is the most common tick-associated illness in the world.[1] This illness is acquired by humans through the bite of *Ixodes* species ticks[2] infected with *Borrelia burgdorferi* sensu lato (Bb) (*Borrelia burgdorferi* sensu stricto, *Borrelia garinii*, and *Borrelia afzelii*). The clinical manifestations of early Lyme borreliosis, including constitutional symptoms such as fatigue, headache, mild stiff neck, arthralgias, myalgias, and fever, are often accompanied by a skin rash, erythema migrans.[3,4] Persistence of Bb can lead to more severe clinical manifestations including secondary annular lesions, meningitis, Bell's palsy, radiculoneuritis, and atrioventricular heart block.[4-6] Furthermore, chronic arthritis may develop weeks to months after infection.[4]

The variability and occasionally protracted nature of Lyme borreliosis makes it difficult to assess the effectiveness of antimicrobial therapy. Optimal treatment regimens, particularly for patients with late-stage or persistent disease, are strongly debated because little is known about the pharmacodynamic interaction between the antimicrobial agent and Bb. In addition, the slow growth rate and fastidious nature of Bb organisms has hindered many investigations by delaying susceptibility testing by conventional methods. Furthermore, it is difficult to accurately determine the viability of Bb by darkfield microscopy, especially when spirochetes become clumped or exhibit impaired motility. In addition, interpretation of growth based on color change can be difficult. For instance, contaminating organisms can cause color changes in Barbour-Stoenner-Kelly (BSK) medium, which would interfere with interpretation of endpoints.

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Oxidation of BSK medium can also kill Bb organisms and produce falsely lowered susceptibility values. Collectively, these factors make conventional methods labor-intensive, time consuming, and difficult to interpret.

Recently, we showed that susceptibility testing of other slow-growing microorganisms such as *Mycobacterium tuberculosis,*[7,8] nontuberculosis mycobacteria,[9] and *Candida albicans*[10] could be rapidly accomplished by using flow cytometry. Results of tests were available in 24 hours or less. In this report, we show that flow cytometry can be used to detect rapidly (18 hours) the minimum bactericidal concentrations (MBC) of antimicrobial agents against Bb.

MATERIALS AND METHODS

Antimicrobial Agents

Amoxicillin and erythromycin (Sigma Chemical Co., St. Louis, MO); cefotaxime (Hoechst-Roussel Pharmaceuticals, Sommerville, NJ); ceftriaxone (Roche Laboratories, Belvidere, NJ); and doxycycline (Pfizer, Inc., Groton, CT) were obtained as standard powders and prepared according to the manufacturer or distributor recommendations. Stock solutions contained 3200 μg of each antimicrobial agent per milliliter of sterile distilled water.

Organisms

Bb isolates 297 (human spinal fluid, Connecticut); B31 (*Ixodes scapularis*, New York); *B garinii* isolates LV4 and PBi (human spinal fluid, Europe); *B afzelii* isolates J1 (*Ixodes persulcatus*, Japan); and BV1 (human blood, Europe) were cultured for 72 hours at 32°C in BSK medium to a concentration of 5×10^7 spirochetes per milliliter. Then, 500 μL samples were dispensed into 1.5 mL sterile vials (Sarstedt Inc., Newton, NC), sealed, and stored at -70°C until used. When needed, a frozen suspension of spirochetes was thawed and used to inoculate fresh BSK. Spirochetes were enumerated using a Petroff-Hausser counting chamber.

Susceptibility Assays

Minimum bactericidal concentration values for 5 antimicrobial agents against isolates of Bb were determined by using a conventional macrodilution technique[11,12] and flow cytometry. Briefly, freshly-prepared stock solutions of each antimicrobial agent were serially diluted (16 to 0.008 μg/mL) in fresh BSK medium. Log phase (72 hours) cultures of Bb isolates were diluted with fresh BSK to a final concentration of 10^6 spirochetes per milliliter. For macrodilution assays, 2 mL of each Bb suspension were combined with 2 mL of each dilution of antimicrobial agent in sterile 13 × 100 mm polystyrene culture tubes (Becton-Dickinson, Lincoln Park, NJ) and incubated at 32°C for 7 days. For flow cytometric assays, 100 μL of each Bb suspension was combined with 100 μL of each dilution of antimicrobial agent in sterile 1.5 mL microcentrifuge tubes (Sarstedt) and incubated at 32°C for 18 hours. Minimum inhibitory concentration values against *Escherichia coli* ATCC 25922 and *Staphylococcus aureus* ATCC 29213 were determined using NCCLS guidelines to ensure appropriate activity of each antimicrobial agent.[13]

Determination of Minimum Bactericidal Concentrations

Macrodilution. Suspensions of antimicrobial agents in which viable spirochetes could not be detected by using darkfield microscopy were subcultured (10% v/v) into 6 mL of BSK containing no antimicrobial agents and incubated for 7 days. The lowest concentration in which viable spirochetes could not be detected by using darkfield microscopy was considered the MBC. Nonmotile Bb organisms were considered nonviable.[14] All assays were performed in duplicate.

Flow cytometry. Following 18 hours of incubation, 100 μL of each assay suspension was transfered into 12 × 75 mm polystyrene culture tubes (Fisher Scientific, Chicago, IL) containing 400 μL of 0.20 μm filter-sterilized phosphate buffered saline (PBS; 0.01 mol/L, pH 7.2) and 50 μL of acridine orange (AO) (5.4×10^{-9} mol/L). Suspensions were gently vortexed and data were acquired using a FACScan single laser flow cytometer (Becton-Dickinson Immunocytometry Systems, San Jose, CA). Initially, viable Bb organisms were detected and differentiated from BSK particles by using side angle light scatter and AO fluorescence intensity parameters. Live gating was performed on dot plots of Bb organisms during data acquisition to exclude debris. Events were acquired for 60 to 90 seconds in the list mode. Fluorescence histograms for each sample were analyzed by using FACScan LYSYS II software. Markers were established for viable Bb organisms based on their binding of AO. The intensity of AO fluorescence and the number of Bb (events) were used to detect bactericidal activity.

Growth Assays

Following flow cytometric analysis, Bb organisms contained in 100 μL of each assay suspension were collected by using 0.2 μm microcentrifuge filter units (Corning Costar Corp., Cambridge, MA) spun at 1500 rpm for 3 minutes. The filters were then washed with 500 μL of sterile PBS to remove residual antimicrobial agents. Following washing, the filters containing spirochetes were resuspended in 500 μL of fresh BSK medium and serially diluted (10-fold) to enumerate survivors. All cultures

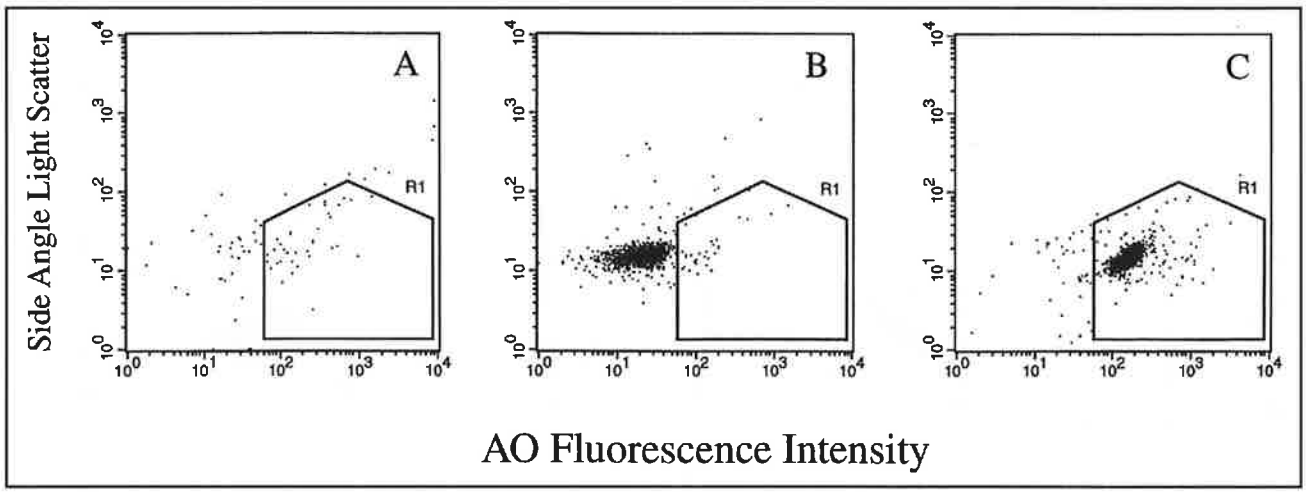

Figure 1. Intensity of acridine orange (AO) fluorescence versus side angle light scatter of B burgdorferi *in the absence (B) or presence (C) of AO in BSK medium. Barbour-Stoenner-Kelly medium without* B burgdorferi *(A) was included as a control.*

were incubated for 14 days and examined periodically for the presence of motile spirochetes by using dark-field microscopy.

RESULTS

Detection of Bb by Flow Cytometry

Viable Bb organisms (Figure 1B) were easily detected and differentiated from particles in BSK medium (Figure 1A) by monitoring side angle light scatter and AO fluorescence intensity parameters. Few background particles were detected in BSK medium (Figure 1A). When Bb organisms were exposed to AO (Figure 1C), they were readily detected and differentiated from Bb organisms not exposed to AO (Figure 1B). When these experiments were repeated with other Bb isolates, similar results were obtained.

Establishment of Gates (regions) for Detection of Viable and Killed Bb

Subsequently, viable organisms were incubated in BSK containing 0.03 µg of ceftriaxone per milliliter. The mean channel of AO fluorescence intensity (MCF) for the ceftriaxone-treated spirochetes increased significantly (Figure 2B) compared with the MCF of AO fluorescence intensity of the drug-free control (Figure 2A). In addition, the number of Bb (events) in the sample treated with ceftriaxone (Figure 2D) was significantly less than the number of spirochetes in the drug-free control (Figure 2C). Similar results were obtained using 0.06 µg of amoxicillin per milliliter, 0.06 µg of cefotaxime per milliliter, 0.25 µg of doxycycline per milliliter, and 0.13 µg of erythromycin per milliliter. When isolates of *B burgdorferi*, *B garinii*, and *B afzelii* were exposed to these antimicrobial agents, uptake of AO by the drug-treated isolates of Bb was significantly more than the uptake of AO by the drug-free controls.

Determination of the Susceptibility of Bb to Antimicrobial Agents by Flow Cytometry

The effects of various concentrations of amoxicillin, cefotaxime, ceftriaxone, doxycycline, and erythromycin were determined based on the intensity of AO fluorescence and the number of Bb (events) after exposure to these antimicrobial agents for 18 hours. In general, the intensity of AO fluorescence increased rapidly when Bb were exposed to increasing concentrations of the antimicrobial agents, while the number of Bb (events) rapidly decreased (Figure 3 A-E). When the number of Bb (events) in samples decreased to approximately 10^3, viable spirochetes were not recovered by subculture to fresh BSK medium. The point at which the AO fluorescence intensity and events curves intersected approximated the MBC of each antimicrobial agent for Bb. These MBC values were 0.06 µg/mL for amoxicillin, 0.06 µg/mL for cefotaxime, 0.03 µg/mL for ceftriaxone, 0.25 µg/mL for doxycycline, and 0.13 µg/mL for erythromycin. The MBC's were confirmed by subculturing washed *B burgdorferi* 297 collected on filters. Results of subculturing experiments confirmed that *B burgdorferi* 297 organisms were killed (data not shown). These values correlated with conventional macrodilution MBCs, with the exception of amoxicillin. The conventional macrodilution MBC for amoxicillin was 16 µg/mL, while the flow cytometric MBC was only 0.06 µg/mL (Table 1). This was likely because of the breakdown of amoxicillin during the long incubation period required for the macrodilution method. Other investigators have shown significant

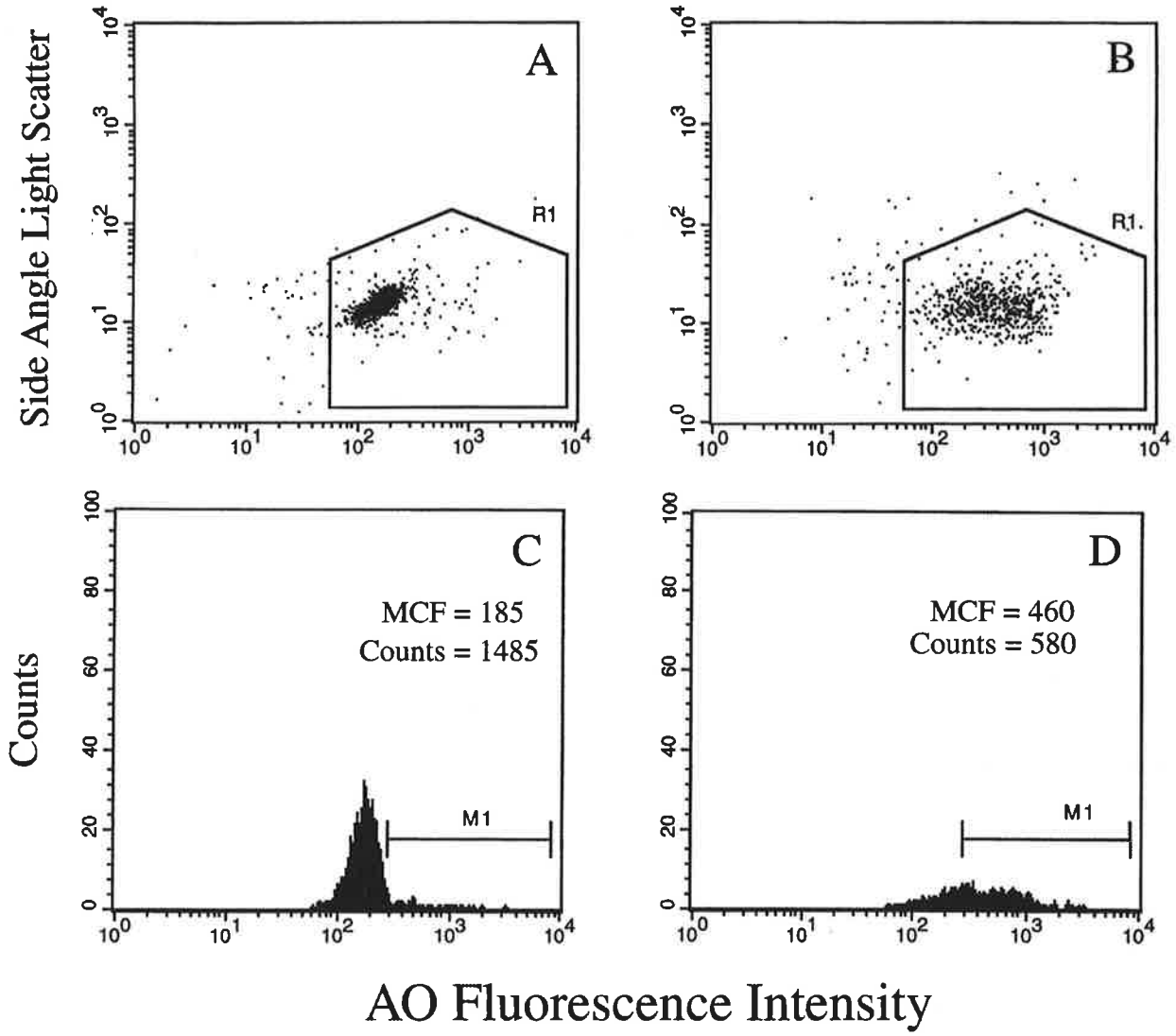

Figure 2. Mean channel fluorescence (acridine orange (AO) fluorescence intensity) versus side angle light scatter of B burgdorferi *in the absence (A) and presence (B) of 0.03 µg/mL ceftriaxone. The lower figures are histogram profiles of the dot plots (A and B).*

Table 1. Comparison of MBC values[a] for five antimicrobial agents against* B burgdorferi *sensu stricto 297 obtained by using flow cytometry and broth macrodilution methods.

Antimicrobial	Minimum borreliacidal concentration[b] (µg/mL)	
	Flow cytometry	Macrodilution
Amoxicillin	0.06	16
Cefotaxime	0.06	0.06
Ceftriaxone	0.03	0.04
Doxycycline	0.25	0.50
Erythromycin	0.13	0.06

[a] *Similar results were obtained when other B burgdorferi sensu lato isolates were tested.*

[b] *Geometric mean of duplicate samples.*

loss (>25%) of activity of doxycycline[21] and ceftriaxone[20,21] after 24 to 72 hours of incubation at 37°C.

Based on these results, an operational definition of susceptibility was established to distinguish changes in intensity of AO fluorescence and numbers of Bb (events), which would accurately predict the MBCs. If the intensity of AO fluorescence of the Bb culture containing antimicrobial agents was 40% more than the intensity of AO fluorescence obtained with the drug-free culture, the MBC was identified. Likewise, a 50% or more decrease in the number of Bb (events) also predicted the MBC. When these flow cytometric definitions were applied to five other isolates of Bb tested with these antimicrobial agents, the MBCs were identified (Table 2). The MBC values

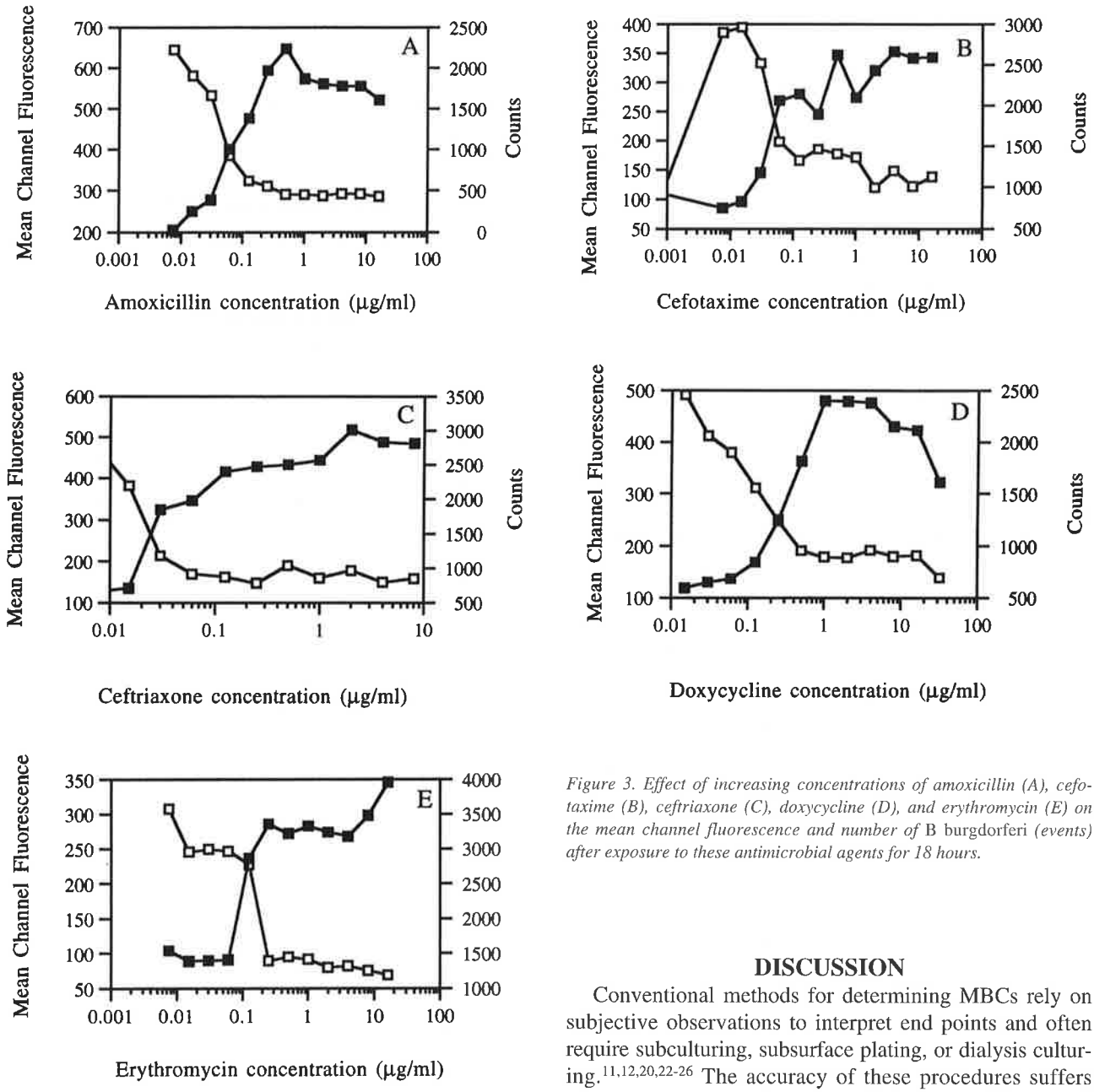

Figure 3. Effect of increasing concentrations of amoxicillin (A), cefotaxime (B), ceftriaxone (C), doxycycline (D), and erythromycin (E) on the mean channel fluorescence and number of B burgdorferi *(events) after exposure to these antimicrobial agents for 18 hours.*

obtained for each isolate were similar and corresponded closely with previously published results using conventional susceptibility testing methods.[11,12,20,22-25] However, the flow cytometric procedure detected some significant differences in MBC values among different Bb isolates. For example, the MBC values of doxycycline against *B burgdorferi* B-31 was 0.13 µg/mL. In contrast, *B garinii* LV4 and *B afzelii* J1 had doxycycline MBC values of 4.0 µg/mL.

DISCUSSION

Conventional methods for determining MBCs rely on subjective observations to interpret end points and often require subculturing, subsurface plating, or dialysis culturing.[11,12,20,22-26] The accuracy of these procedures suffers when organisms replicate slowly because of increased incubation times and the instability of antimicrobial agents. A flow cytometer is capable of simultaneously collecting quantitative and qualitative data by detecting individual cells. This allows for rapid and precise identification and characterization of cells contained within a heterogenous population. In addition, the viability of microorganisms contained in a population can be determined by monitoring the uptake of fluorescent dyes.[7-10,15-19] These characteristics of flow cytometry have led investigators to explore its use as an alternative approach to conventional susceptibility testing methods. Results of these studies

Table 2. Flow cytometric MBC values for five antimicrobial agents against **B burgdorferi** *sensu stricto,* **B garinii,** *and* **B afzelii** *isolates.*

Antimicrobial	Minimum Borreliacidal Concentration* (μg/mL)				
	CFT	CTX	DOX	AMX	ERY
B burgdorferi ss					
B31	0.04	0.06	0.13	0.13	0.13
B garinii					
LV4	0.02	0.06	4	1	1
PBi	0.04	0.13	0.50	0.06	0.02
B afzelii					
BV1	0.08	0.13	0.50	2	0.06
J1	0.02	0.06	4	2	0.03

**Geometric mean of duplicate samples.*

Abbreviations: CFT = Ceftriaxone; CTX = Cefotaxime; DOX = Doxycycline; AMX = Amoxicillin; ERY = Erythromycin.

have demonstrated that flow cytometry is useful for determining the antimicrobial susceptibilities of slow-growing bacterial and fungal pathogens.[7-10,15-18]

In this investigation, we developed a flow cytometric procedure to determine MBCs of Bb more rapidly. The ability to obtain susceptibility results in 18 hours is a significant improvement over the 13 to 15 days required by conventional Bb susceptibility assays.[11,12,20] By monitoring intensity of AO fluorescence and the number of Bb (events), flow cytometry could easily discriminate between living and nonviable Bb. Using a 40% increase in AO fluorescence intensity or a 50% decrease in the number of Bb (events) to predict MBCs appeared accurate. When concentrations of antimicrobial agents were below the MBC values, AO fluorescence intensity and the number of Bb (events) remained nearly identical to those values obtained with spirochetes incubated in drug-free BSK medium. Although testing of more isolates of Bb might fine tune the determination of cut-off values, these values are unlikely to differ significantly from our selected values.

In addition, the accuracy of susceptibility testing of Bb may improve by performing the flow cytometric assay. We detected significant variations in the MBCs of antimicrobial agents among several Bb isolates. The ability of flow cytometry to rapidly determine MBC concentrations of antimicrobial agents against Bb should improve the correlation between in vitro susceptibility results and clinical efficacy. This will be especially important when evaluating antimicrobial agents that are unstable in solution or have been newly developed as potential therapies for Lyme borreliosis. In addition, the ease and objectivity of the flow cytometric procedure makes it suitable for determining MBCs against large numbers of Bb isolates.

In conclusion, we demonstrated that susceptibility testing of Bb could be accomplished by using flow cytometry to monitor the uptake of AO and enumerate viable and killed Bb organisms in drug-free and antimicrobial agent-containing medium. Most importantly, the flow cytometric susceptibility test was rapid, reproducible, and simple to perform.

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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.*

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

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.

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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Tc-99m HMPAO Brain SPECT Imaging in Chronic Lyme Disease

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ABSTRACT

Patients with Lyme disease may experience neuropsychiatric problems that persist even after standard courses of antibiotic therapy. Objective detection of neuroimaging brain abnormalities can be helpful to the clinician by demonstrating either focal or diffuse deficits, thereby supporting a CNS origin to the neuropsychiatric problems. To examine the potential utility of SPECT brain imaging in the evaluation of chronic Lyme disease (CLD), two questions were addressed: 1) Are SPECT brain scans abnormal in CLD patients with neuropsychiatric findings? and 2) If abnormal, are the perfusion abnormalities specific for CLD?

SPECT brain scans of 19 patients with CLD and 14 non-CLD patients with other neurological diagnoses resulting in perfusion abnormalities were evaluated in a blinded read without reference to clinical status. Scans were randomly ordered for interpretation by three experienced SPECT readers. Final interpretation was arrived at by consensus. Scans were interpreted as normal, abnormal-focal hypoperfusion, or abnormal-diffuse hypoperfusion. Hypoperfusion was described as homogenous or heterogenous. Results were analyzed as percent normal or abnormal and pattern of abnormality.

CLD SPECT scans were interpreted as abnormal in 14 of 19 (74%) scans, each characterized as heterogeneous with or without globally decreased perfusion. One CNSLD scan showed a focal lesion. CLD patterns could be distinguished from non-LD patients with a diagnosis of Alzheimer's or Moya-Moya disease but not from non-LD patients with a diagnosis of Creutzfeldt-Jacob disease, Lupus, cerebral vasculitis, or chronic fatigue syndrome. Of the 14 patients who had brain MRI scans, only 2 (14.3%) were abnormal, revealing white matter hyperintensities.

These findings suggest that brain SPECT may be a more sensitive tool than MRI for identifying brain abnormalities in CLD, but that the heterogenenous pattern is not specific to CLD.

Key words: Lyme disease, SPECT, brain imaging, profusion

INTRODUCTION

Patients with chronic Lyme disease (CLD) may have persistent neuropsychiatric signs and symptoms.[1-3] The identification of objective markers of brain involvement in this patient population is critical: a) to support the hypothesis that the neuropsychiatric problems are related to a diffuse brain disease; and b) to provide evidence of physiologic change that may correlate with reduced symptoms following treatment. A variety of imaging modalities including CT and MR have had limited value in the evaluation of CLD patients. SPECT brain imaging is a potential tool for establishing the presence of brain changes in these patients. In particular, if SPECT brain scans reveal perfusion abnormalities, then such findings would be helpful in establishing the physiological basis for the clinical presentation. Preliminary reports suggest that brain SPECT studies of patients with CLD who present with neurological and/or psychiatric complaints[4-6] are often abnormal.

To examine the potential utility of SPECT brain imaging in the evaluation of the patient with CLD, we performed a retrospective study to address two questions.

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First, do CLD patients with neurological and/or psychiatric findings have abnormal SPECT brain scans? Second, if SPECT scans are interpreted as abnormal, are the perfusion abnormalities specific for CLD?

MATERIALS AND METHODS

Subjects

Lyme disease patients. SPECT brain scans of 19 patients (mean 35.6 years, SE 2.8, 9M/10F) with a diagnosis of CLD who were referred to the Nuclear Medicine Division, Department of Radiology, New York Presbyterian Medical Center prior to 11/19/96 were evaluated in a blind read. The clinical work-up and diagnosis of CLD was made by the referring physicians.

Based on clinical records and examination the diagnosis of CLD was confirmed by ensuring that all patients met the following criteria: a) a multisystem illness affecting the neurologic, articular, cardiac, and/or dermatological systems; b) a positive Western blot (IgG or IgM) for Lyme disease; and c) exposure to a Lyme endemic area. Patients in this sample had Western blot assays performed at one or both of the following two laboratories: BBI Clinical Laboratories (New Britain, CT) and/or University Medical Center Health Sciences Center, State University of New York at Stony Brook (Stony Brook, New York). The standard for Westem blot interpretation varied depending upon the individual laboratory.

Chart review showed that each patient had constitutional, musculoskeletal, and neuropsychiatric symptoms. The most prominent complaints among the 19 patients were:

Constitutional—fatigue (100%), insomnia (52.6%), night sweats (26.3%).

Musculoskeletal—migrating large joint pains (84.2%), neck pain (52.6%), arthritis (15.8%).

Neuropsychiatric—cognitive complaints (eg, memory, attention) (94.7%), headache (89.5%), paresthesias (57.9%), tinnitus (57.9%), depression (52.6%), blurry vision (52.6%), photophobia (26.3%).

It was documented in the physician's chart that 31.6% of the patients had an erythema migrans rash. Only 26.3% of the patients recalled a tick bite. All CLD patients in this study had undergone prior antibiotic treatment for Lyme disease. The majority of patients had been ill for more than a year before Lyme disease was diagnosed and treated (median 88 weeks).

MRI, EEG, CSF, and neuropsychological test data were available on some of the patients: 2 of 14 patients (14.3%) had abnormal brain MRIs (white matter hyperintensities); 1 of 8 patients had an abnormal EEG; 6 of 11 patients (54.5%) had abnormal spinal fluid (elevated protein, lymphocytosis, *Borrelia burgdorferi* PCR, and/or elevated Lyme titer). None of these 6 patients met criteria for intrathecal antibody production; 10 of the 19 patients had a battery of neuropsychological tests with each of the 10 individuals demonstrating clinically significant cognitive deficits.

Non-Lyme disease patients. SPECT brain images of 14 non-LD patients were selected from among the recent scans performed in the Nuclear Medicine Laboratory of the Nuclear Medicine Division of the Radiology Department at the New York-Presbyterian Hospital. These scans were interspersed among the scans obtained on the CLD patients as described below. Non-LD patients ranged in age from 29-47 years (mean 46 yrs). Clinical diagnoses in these patients were: presumed Alzheimer's disease-2; cerebral vasculitis-4; chronic fatigue syndrome-3; Creutzfeldt-Jacobs disease (pathologically confirmed)-l; Lupus-2; and vascular insufficiency-2. The 3 patients with chronic fatigue syndrome were seronegative for Lyme disease according to the referring physician. Because this was a clinical series of scans, the medical work-up of these other 11 patients with other neurologic illnesses was unknown to us. In other words, we do not know whether or not these patients had been tested for Lyme disease.

SPECT Imaging Studies

Prior to their SPECT examination, LD patients were told not to use caffeine and nicotine for at least 2 hours prior to the study. Patients were administered an IV injection of Tc-99m-hexamethlypropyleneamine (Tc-99m-HMPAO) in doses ranging from 555 to 814 megabecquerel (15-22 millicuries) while in a supine position with eyes open in a low-stimulation environment. Imaging was begun 40 minutes post injection.

Images were acquired on a triple-headed SPECT camera (Picker Prism 3000, Cleveland, OH) following a previously validated rapid acquisition sequence (RAS) imaging protocol.[6] The details of image acquisition and processing are described in the Appendix. Axial, coronal, and sagittal Picker light box images were reviewed using the Picker step-10 color scale. Studies were normalized to mean cerebellar counts. Background counts were set to the scalp activity (approximately 10% background subtraction). If cerebellar disease was evident then the study scale was normalized to the deep grey matter. The color scale was consistent across all patients.

Image Interpretation

The 33 SPECT brain scans (19 CLD and 14 non-LD patients) were randomly ordered for a blinded interpretation by 3 experienced SPECT readers (RVH, RST, JJP). Final interpretation was arrived at by consensus. No clinical information was available to the readers when the

images were subjected to interpretation. Scans were interpreted as normal if there were no areas of hypo/hyperfusion. An area of abnormal perfusion was defined as nonanatomic cerebral hypoperfusion that was ≤ 60% of the cerebellar or deep grey matter perfusion. Perfusion abnormalities were defined as: a) focal if the hypoperfusion was confined to one brain lobe, or b) diffuse if more than one lobe showed hypoperfusion. Patterns of hypoperfusion are described as either homogenous or heterogenous. A homogeneous pattern was defined as diffuse hypoperfusion throughout the cerebrum. A heterogeneous pattern was defined as multiple or diffuse areas of hypo perfusion interspersed with areas of normal perfusion.

Data Analysis

Results of the consensus read of the SPECT scans were subsequently analyzed to determine the percent of scans interpreted as normal or abnormal and types of abnormal patterns observed.

RESULTS

SPECT scans were interpreted as abnormal in 14 of the 19 (74%) patients with CLD. In 13 of the 14 patients, a SPECT scan pattern was characterized by diffuse cortical heterogeneity with or without globally decreased perfusion. A focal lesion was seen in 1 abnormal scan. The patterns in the CLD scans could not be accurately distinguished from the scan patterns observed in patients with Creutzfeldt-Jacobs disease (1/1 incorrect), Lupus (1/2 incorrect), cerebral vasculitis (2/4 incorrect), and chronic fatigue syndrome (3/3 incorrect). This heterogeneous pattern was not seen in the 2 Alzheimer's patients and the patient with Moya-Moya disease. Representative SPECT scans for CLD and non-LD patients are shown in the Figure.

Of the 11 patients on whom CSF results were available, 6 had an abnormal CSF of whom 4 also had an abnormal SPECT, and 5 had a normal CSF of whom 4 had an abnormal SPECT. Of the 10 patients who had neuropsychological testing and who demonstrated cognitive deficits, 6 of the 10 had abnormal brain SPECT scans. Of the 14 patients on whom MRI results were available, 12 had normal brain MRIs but 9 of these 12 had abnormal SPECT scans.

DISCUSSION

Lyme disease is the most common vector-borne infectious disease in the United States. It is caused by the bacterium, *Borrelia burgdorferi,* a spirochete.[7] The disease may cause acute-subacute (days to weeks), and chronic (months, years, and even decades) bouts of insidious, multisystem signs and symptoms of infection. The most commonly reported symptoms are musculoskeletal, dermatologic, neurologic, psychiatric, and cardiac.[8]

Neurologic/psychiatric signs and symptoms may occur in up to 40% of patients shortly after infection. Neurologic findings may include Bell's palsy, acute meningitis, acute encephalitis, or motor or sensory peripheral nervous dysfunction. Memory loss, inattention, slow processing speed, anxiety, depression, paranoia, and severe mood swings have been reported as neuropsychiatric manifestations of central nervous system involvement.[3]

Reports suggest that not all patients with Lyme infection become seropositive.[9,10] There is a need for "objective" tools to aid in diagnosis, and to gauge the efficacy of antibiotic therapy in patients with neuroborreliosis. Such tools include neuropsychological testing and noninvasive imaging procedures. MR imaging in CLD reveals a wide variety of noncortical abnormalities. Reports show that the percent MR abnormalities vary between 10% and 40% in LD patients with neurologic signs and symptoms.[3,11,16] In our sample, 14.3% had abnormal MR scans, each demonstrating white matter hyperintensities. Although not a sensitive test in detecting abnormalities among patients with CLD, MRI is a very useful technique for excluding other diseases such as neoplasms, vascular or congenital malformations, and chronic extra-axial bleeds that could result in clinical presentations like those of CLD.

SPECT brain imaging is another noninvasive imaging modality that may have utility for assessing CNS involvement associated with Lyme disease. Das et al reported that 51.4% of 35 suspected CNS Lyme disease patients showed SPECT abnormalities.[4] The pattern described was that of heterogenous decreased cortical perfusion in 83% of cases with abnormal scans. We report a similar finding, with 14/19 scans (74%) being abnormal. The most prominent pattern was that of a diffuse heterogenous reduction of cortical perfusion. At the present time there is no satisfactory explanation for the pattern observed in LD. The cortical abnormalities seen on SPECT scans may represent a secondary response to involvement of subcortical white matter. These abnormalities may also be caused by vasculitis.[16] Logigian et al,[5] using quantitative brain SPECT analysis, reported multifocal white matter perfusion abnormalities in patients with LD.

The pattern of diffuse cortical heterogeneous hypoperfusion reported in the present study is similar to that seen in patients with Creutzfeldt-Jacob disease, primary cortical vasculitis, Lupus, and chronic fatigue syndrome. This pattern has also been reported for patients with AIDS infection and polysubstance abuse.[17,21] However, the pattern is distinct from that of Alzheimer's disease or the watershed hypoperfusion in Moya-Moya disease. In Alzheimer's disease, for example, we would typically see decreased perfusion in the temporo-parietal regions of the brain in both hemispheres with sparing of the sensory-motor strip.

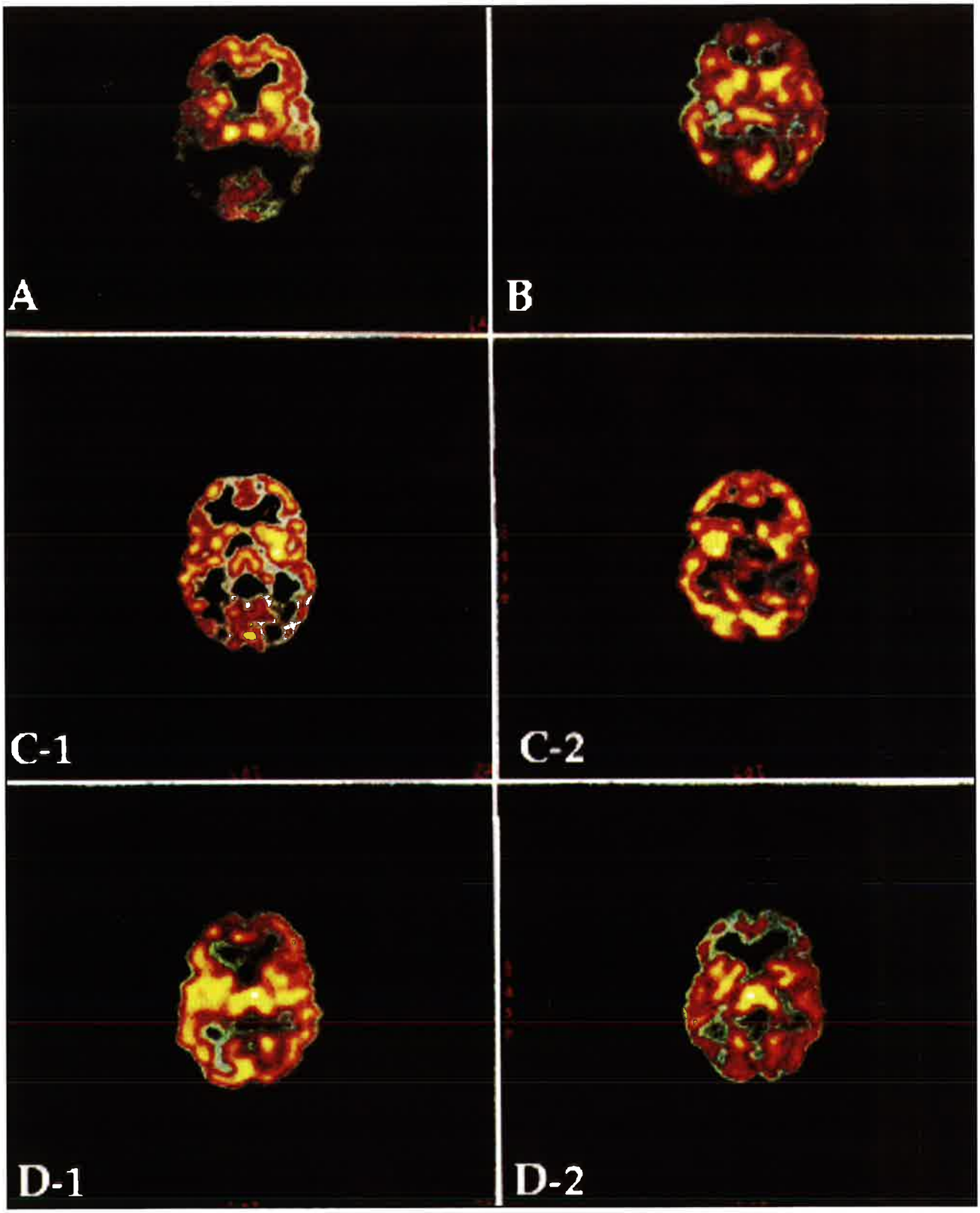

*Figure. Representative examples of SPECT studies used in the blind read. (**A**) Alzheimer's disease; (**B**) cerebral vasculitis; (**C-1**) baseline—Lyme disease patient; (**C-2**) same patient after treatment showing improvement; (**D-1**) baseline—Lyme disease patient; and (**D-2**) same patient after treatment whose condition worsened.*

Our findings suggest that brain SPECT scans may be an objective and useful tool for visualizing the cortical changes that may be correlated with the central nervous system manifestations of Lyme disease. It must, however, be emphasized that the finding of a "normal" brain SPECT scan is not sufficient to "rule out" the presence of CNS Lyme disease. Likewise, an abnormal SPECT scan by itself does not suffice to establish a diagnosis of Lyme disease, but with other clinical and laboratory data may point to CNS involvement when the diagnosis of Lyme disease cannot be established by other means. Abnormalities revealed in the SPECT scans are not typically seen with standard anatomic imaging procedures such as MRI or CT.

Although a significant number of scans of the CLD patients revealed abnormalities, these abnormalities could not be distinguished from other disease entities that show diffuse heterogenous hypoperfusion. Our findings, therefore, demonstrate that SPECT brain imaging can be helpful in identifying the presence of a disease process that affects the brain diffusely, but the lack of specificity in the heterogeneous pattern limits its usefulness in distinguishing one diffuse brain disorder from another. Our study does not answer the question of whether brain SPECT scans can be used to differentiate patients with primary psychiatric disorders from patients with Lyme disease accompanied by secondary psychiatric disorders because none of our control patients had a primary psychiatric disorder as the main diagnosis.

This study by nature of its retrospective design has limitations that preclude definitive conclusions. For example, although we presumed that the non-Lyme disease patients did not have Lyme disease based on the referring physician's clinical information, this is not certain given that we did not conduct Lyme tests on these patients. This issue is particularly problematic regarding patients with chronic fatigue syndrome whose symptom constellation is quite like that of patients with CLD. Although the referring physician assured us that patients with chronic fatigue syndrome had negative Lyme serologies, we still could not be certain that they did not have Lyme disease as the trigger to their chronic fatigue given the problems with serologic sensitivity in Lyme disease.

Further research, combining systematic neurologic/neuropsychologic testing with serial SPECT scanning is needed to further elucidate the role of SPECT scanning in Lyme disease and to assess the effects of various therapeutic interventions for CLD.

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APPENDIX

SPECT images were obtained by acquisition of four RAS data sets with a Leuhr-Fan beam collimators (Picker). Each data set was a 360° continuous mode. Acquisition was comprised of 120 total projection images (40 projection images per detector). The radius of rotation was equal to or less than 14 cm, with a hardware zoom-magnification factor of 1.0. Each projection image was 7.5 seconds with a total acquisition time of approximately 20 minutes. Axial images were aligned parallel with the canthomeatal line and the corona/sagittal planes were aligned perpendicular to the axial rotation of the camera. Images were acquired into a 128 × 128 digital computer matrix. The four rapid acquisitions sequences were subsequently summed together and reconstructed with filtered backprojection and attenuation correction of 0.11 (Picker). A low-pass (Butterworth, Picker) filter was used with a fifth order slope and the cut-off frequency of .35–.45 cycles per pixel. Single pixel width transaxial images were used to reconstruct the coronal and sagittal planes. All image planes were displayed as 3 pixel width (6.6 mm) thick slices. The SPECT system spatial resolution was 0.78 cm (FWHM).

Case Report: Lyme Disease and Complex Partial Seizures

Robert C. Bransfield, MD

ABSTRACT

A case of complex partial seizure disorder associated with late stage neuropsychiatric Lyme disease is presented. The patient showed a progressive development of somatic, cognitive, psychiatric, and neurologic symptoms. Reliance upon a conservative criteria for the interpretation of immunological testing caused an initial delay in diagnosis and treatment, resulting in more severe symptoms including a complex partial seizure disorder. Early diagnosis and treatment of Lyme disease is suggested to prevent the development of more severe sequelae, such as complex partial seizure disorder. When patients present with a complex partial seizure disorder and a multisystem illness, Lyme disease should be considered in the differential diagnosis.

Key words: seizures, Babesiosis, neuroborreliosis, cognitive

INTRODUCTION

Seizure disorders are sometimes a manifestation of late stage neuropsychiatric Lyme disease. There are a number of references to this association in the medical literature.[1-17] A case history is presented to describe the emergence of a seizure disorder in association with late stage Lyme disease.

CASE REPORT

A 46-year-old female patient lived in a Lyme endemic area and recalled an incident in which she and her 8-year-old daughter sustained multiple tick bites at the same time approximately 5 years previously (the daughter was subsequently diagnosed with Lyme disease). The patient did not recall any ECM-like bulls eye rash or flu-like illness at the time. However, she noticed the gradual onset of increasing symptoms over the next two years which initially included arthralgias of the thumbs and aching hands bilaterally, night sweats, shortened menstrual cycles, insomnia, and unexplained irritability and anger.

Two years after the tick bite, the patient sprained her ankle and had difficulty healing from this injury. She also noted the uninjured ankle was hurting as well.

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Following the ankle injury, there was a rapid increase in the development of symptoms including memory impairments; spelling difficulties; loss of executive functioning; becoming lost in familiar places; depression; numbness and tingling of the left side of her face; pain under her left eye; twitching of her left eye; tinnitus; ear pain; myoclonic jerks; jerking movements of the left shoulder; involuntary movements of her fingers, hands, arms, and legs; burning pain of her right hip; lower back pain on her right side; nerve pain; numbness and tingling of both legs; restless leg syndrome; a pulling in of the right foot followed by a jerking of the right leg; involuntary toe movement; chills; and fatigue.

She saw several physicians and had multiple diagnoses including an adjustment reaction from a fertility problem, multiple sclerosis, Huntington's, and moving toe and painful leg syndrome.

She was referred to a neurologist who ordered serology testing for *Borrelia burgdorferi* antibodies. A reactive enzyme immunoassay (1.11) was confirmed by repeat analysis (> 0.99 positive), IgM Western blot was reactive (39 and 41 kd bands), and IgG Western blot was interpreted as negative (23, 28, 41, 93 kd bands were present) by Smith Kline Beecham Labs. The testing was considered negative since there were only four bands on the Western blot IgG.

A magnetic resonance imaging (MRI) scan was also negative. The strobe light during an electroencephalogram (EEG) resulted in a seizure-like episode. Although spikes were seen on the EEG, no seizure was recorded.

During a subsequent lumbar puncture, an apparent complex partial seizure occurred.

A second MRI scan a year later demonstrated scattered foci of abnormal signal within the periventricular white matter, more confluent in the periatrial region. However, a second physician interpreted this MRI as normal.

Subsequently, a family physician diagnosed the patient with Lyme disease based upon clinical grounds and started treatment with intravenous ceftriaxone. A second seizure occurred during intravenous treatment. There was a significant clinical improvement with 10 weeks of intravenous treatment. After discontinuing the intravenous antibiotics, the patient relapsed and was treated with a second 10-week course of ceftriaxone. The patient again improved but more slowly. The patient recorded her symptoms and reported improvement of cognitive and emotional symptoms. After discontinuing the second course of intravenous antibiotics, there was a return of myoclonic jerks, and later seizure activity on a daily basis. Seizures were triggered by caffeine, light flickering through a row of trees on the highway, exercise, or during symptom flares associated with antibiotic treatment (apparent Jarish–Herxheimer reactions). They sometimes began with blurred vision, followed by increasing tinnitus, drowsiness, and a sense that her body was floating. During these episodes, her right arm stiffened accompanied by a twitching of her right toes, which progressed to her feet and calf muscles. The right foot then bent inward, and her legs began jerking. After her legs stopped jerking, her head turned from side to side as far as her head could turn. After the head movements stopped, her abdomen contracted, as if doing sit-ups. These contractions forced the air out of her lungs. After several minutes, the seizures stopped. She felt tired after these episodes.

The patient was referred to another physician experienced in the evaluation and treatment of Lyme disease. The Lyme IgG/IgM antibody test was equivocal at 1.03 with a reactive cut off of 1.2. Lyme Western blot testing for IgM was positive with 23-25, 31, 37, 41, and 58 Kd bands. IgG was positive with 23-25, 28, 31, 34, 41, 58, 73, and 83 kd bands (Ingenex, Menlo Park, CA).

The *Babesia microti* IgM titer was negative, and the IgG titer was reactive at 1:80. There was a confirmation with positive *B microti*-in situ (RNA), multiple merozoites only (Ingenex). No blood smear was reported. Human granulocytic ehrlicheosis (HGE) titer was 1:40 for IgM and 1:80 for IgG. Human monocytic ehrlicheosis (HME) titer was 1:80 for IgM and 1:80 for IgG (Ingenex). The findings of the *Babesia*, HGE, and HME testing added support for the presence of tick-borne diseases. However, it should be noted that a negative blood smear and nonreactive IgM test of *Babesia* antibody does not support the diagnosis of acute babesiosis.

A psychiatric assessment performed 6 months after intravenous antibiotic treatment was discontinued demonstrated the following signs and symptoms: decreased ability to sustain attention span, decreased ability to allocate and prioritize attention, easily distracted by frustration, auditory hyperacusis, visual hyperacusis, decreased working memory, decreased short-term memory, slowness retrieving words and names, becoming lost in familiar locations, letter reversals, spelling errors, word substitution errors, depersonalization, poor concentration, "brain fog"(slowness and inaccuracy of processing), decreased capacity to plan and prioritize, obsessive thoughts, mental apathy, decreased frustration tolerance, sudden abrupt mood swings, exaggerated startle reflex (including acoustic startle), explosive anger, decreased social functioning, decreased job performance, family problems, compensatory compulsions, dropping objects from her hand, crying spells, depression, panic attacks, generalized anxiety, not well rested in the morning, mid and early insomnia accompanied by seizures, episodes of anorexia and weight loss, episodes of overeating accompanied by weight gain, decreased libido, decreased capacity for pleasure, menstrual irregularity, intolerance to cold, decreased body temperature (average 97.6°F), night sweats, chills, cervical radiculopathy, tension headaches, intolerance to bright light and fluorescent lights, conjunctivitis, eye pain, dry eyes, left sided Bell's palsy, tinnitus, hearing loss, dizziness, low threshold for motion sickness, choking on food, absence and complex partial seizures, numbness, tingling, sensory loss, burning, stabbing sensations, paresis, tremor, twitching, muscle tightness, restless leg, myoclonic jerks, herniated discs, equivocal Rhomberg, a sensation of being bit by fleas, vibration sensations on the bottom of the feet, a sensation of an outer ear infection, tightness and crepitations of joints, periostitis of the right tibia, myalgia, tarsal tunnel syndrome, chest pain, racing pulse, shortness of breath, cough, sinusitis confirmed by MRI, recurrent urinary track infections, and vaginal pain.

It was noted that the symptoms gradually progressed over a period of 5 years since the initial onset of the illness. Symptoms fluctuated throughout the day and were increased perimenstrually and by stress. Antibiotics initially increased these symptoms (including the seizures) followed by a subsequent improvement. Symptoms were noted to increase when antibiotics were stopped.

The patient has subsequently improved in response to a complex treatment approach. The current treatment is clarithromycin, paroxetine HCI, gabapentin, clonazepam, magnesium and B_{12} shots (one a week), and doxycycline 300 mg at dinner.

DISCUSSION

This patient presented with a systemic illness, and progressive development of increasing somatic neurological, cognitive, and psychiatric symptoms. Although the clinical signs and symptoms were compatible with a diagnosis of Lyme disease, and could not be explained by any other diagnostic entity, the diagnosis was not confirmed by the immunological criteria many consider necessary for the diagnosis of Lyme disease. The diagnosis of Lyme disease is based upon clinical grounds. However, laboratory testing may or may not confirm the diagnosis. This patient had some tests positive for 4 tick-borne diseases—Lyme disease, babesiosis, HME, and HGE. This suggests that the patient was exposed to tick-borne diseases. The question exists whether other unknown tick-borne diseases might also be present. The presence of these diseases might be considered coinfections. If there is a synergistic interaction between these microbes, it would be considered an interactive coinfection. However, it is difficult to demonstrate such interactions when the copresence of such microorganisms and their effect on the host is not well understood.

The patient had symptoms that could be compatible with babesiosis and some laboratory findings supported this diagnosis. However, there are no clearly defined chronic central nervous system symptoms associated with chronic babesiosis.

Babesiosis is noted to have similarities to malaria. Cerebral malaria has been extensively studied and is associated with a number of mental symptoms including seizures, depression, memory deficits, irritability, and aggression.[18,19] Although the presence of both *B microti* and *B burgdorferi* cannot be proven, neither can one rule out the possibility that they contributed in some manner to the development of the seizures or other neuropsychiatric symptoms. Further investigation is needed in this area.

CONCLUSION

This case demonstrates the development of a complex partial seizure disorder in association with late stage neuropsychiatric Lyme disease. Early diagnosis and treatment is suggested to prevent the development of this and other manifestations of neuroborreliosis. Lyme disease should be considered in the assessment of patients presenting with the recent onset of a complex partial seizure disorder.

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INFORMATION FOR CONTRIBUTORS

Journal of Spirochetal and Tick-borne Diseases

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The following guidelines are in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" and the International Committee of Medical Journal Editors (the "Vancouver Group") statement, agreed at the January 1993 Meeting.

The *Journal of Spirochetal and Tick-borne Diseases* publishes quarterly reviews and original work studies about any aspect of spirochetal and tick-borne diseases. The primary purpose is to broaden our understanding of spirochetal and tick-borne diseases. Special focus is given to Lyme borreliosis (also known as Lyme disease), as the most prevalent spirochetal and tick-borne disease. The clinical topics may involve all medical disciplines, nursing, and pharmacy, as well as the social, ethical, and biological features of spirochetal and tick-borne diseases.

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PROGRAM AGENDA

Saturday, March 25, 2000
8:00 AM -5:15 PM

- **Keynote Speaker: Richard Blumenthal, Attorney General of Connecticut**
- West Nile Virus: Epicenter to Epidemic and Expectations in 2000—T McNamara, DVM, Natl Wild Conserv/Bronx Zoo
- West Nile Virus in Connecticut—J Anderson, PhD, Conn Agri Exp Station
- Overview of Human Ehrlichioses and Rocky Mountain Spotted Fever in the US—C Padduck, MD, CDC
- Coinfections—L Magnarelli, PhD, Conn Agri Exp Station
- Lyme Disease in the South—J Oliver, PhD, Georgia Southern Univ
- Analysis of Southern Borrelia—A James, PhD, CDC
- Babesiosis—P Krause, MD, Univ Conn Sch Med
- Preliminary In Vitro and In Vivo Findings of Hyperbaric Oxygen Treatment in Experimental *Borrelia burgdorferi* Infection—C Pavia, PhD, NY Med Coll Sch Med, NYCOM Microbio Immun Lab NYIT
- Immunity Against Host-Adapted *Borrelia burgdorferi* in the Rabbit—J Miller, PhD, UCLA Sch Med
- Immunologic Aspects of Vlse, a *Borrelia burgdorferi* Antigenic Variation Protein—S Norris, PhD, Univ Tex Med Sch
- An Immunodominant Peptide of *Borrelia burgdorferi* Vlse: Role in Diagnosis and Pathogenesis—M Philipp, PhD, Tulane Univ Sch Med
- Antibiotic Treatment of Lyme borreliosis: A Review of Results with Dogs—R Staubinger, DVM, PhD, Cornell Univ Sch Vet Med
- A *Borrelia burgdorferi* Repetitive Antigen that Confers Protection Against Experimental Lyme Disease—R Skare, PhD, Texas A & M Univ Hlth Sci Ctr
- Use of Borreliacidal Assay in the Serodiagnosis of Lyme Disease—R Schell, PhD, Univ Wiscon Sch Med
- Lyme Neuroborreliosis: Role of PCR and Culture in the Diagnosis and in the Confirmation of Relapse after Antibiotic Treatment—J Oski, MD, PhD, Turku Univ Ctrl Hosp, Finland
- Laboratory Testing Panel—R Tilton, PhD, BBI Clin Labs; J Shah, PhD, Igenex Labs; R Schell, PhD, Univ Wiscon Sch Med; M Golightly, MD, SUNY Stony Brook Sch Med; E Mordechai, PhD, Med Diagn Labs; S Schutzer, MD, UMDNJ

Sunday, March 26, 2000
8:00 AM - 5:00 PM

- **Keynote Speaker: Willy Burgdorfer, National Institutes of Health**
- Characterization of an Immune Evasion System in Lyme Disease Spirochetes—R Marconi, PhD, Med Coll Virg
- Environmental Regulation of Gene Expression in *Borrelia burgdorferi*—S Samuels, PhD, Univ Mont Sch Med
- Matrix Metalloproteinases in Lyme Disease Pathogenesis—G Perides, MD, Beth Israel Deaconess Med Ctr
- Interleukin-10 Regulation During Acute Lyme Arthritis in Dogs—R Staubinger, DVM, PhD, Cornell Univ Sch Vet Med
- T-Cell Response—A Marques, MD, NIH
- Protection Against Tick-Transmitted Lyme Disease in Dogs Vaccinated with a Multiantigenic Vaccine—A Frey, PhD, NYU Sch Med
- OspA Vaccine Update, Including Serologic Results and Range of EM Rashes—D Parenti, MD, SmithKline Bio
- Atypical EM and Acute Lyme Disease—E Masters, MD, Reg Primary Care Phys
- Neurologic Lyme Disease in Children and Adolescents—D Pietrucha, MD, Cornell/NY Hosp, Jersey Shore Med Ctr
- Cognitive Deficits in Children with Chronic Lyme and the Public Health/Educational Implications—M Rissenberg, MD, Columbia Univ Sch Med
- Neurologic Lyme Disease in Adults—P Coyle, MD, SUNY Stony Brook Sch Med
- Neuroimaging in Neuropsychiatric Lyme Disease: Uses, Abuses, and the Future—B Fallon, MD, Columbia Univ Coll Phys Surg
- Pharmacologic Properties of Antibiotics and Their Relevence to Lyme Disease—S Donta, MD, Boston Univ Sch Med
- Treatment Roundtable—L Fein, MD, Morristown Mem Hosp; K Leigner, MD, Westchester Med Ctr; S Donta, MD, Boston Univ Sch Med; D Pietrucha, MD, Cornell/NY Hosp, Jersey Shore Med Ctr; J Burrascano, MD, Southampton Hosp