0193–953X/98 $8.00 + .00

THE UNDERDIAGNOSIS OF NEUROPSYCHIATRIC LYME DISEASE IN CHILDREN AND ADULTS

Brian A. Fallon, MD, MPH, Janice M. Kochevar, NP, Andrea Gaito, MD, and Jenifer A. Nields, MD

Lyme disease is a tick-borne illness caused by the spirochete *Borrelia burgdorferi*. Reported throughout the United States, the greatest incidence of Lyme disease occurs in certain areas, such as the Northeast, the upper Midwest, and the Pacific Coastal states. It has been dubbed "The New Great Imitator" because, like another spirochetal illness neurosyphilis—the original Great Imitator, Lyme disease has a vast array of multisystem manifestations, including neuropsychiatric ones.[18] Failure to recognize Lyme disease early in its course can result in the development of a chronic illness that is only temporarily or partially responsive to antibiotic therapy. The goal of this article is to present the typical and atypical manifestations of Lyme disease in children and adults in order to help the clinician more rapidly unmask the correct diagnosis behind the puzzling presentations of some patients.

THE DIAGNOSTIC PROBLEM

Whenever a disease exists for which serologic tests are unreliable in determining the presence or absence of the disease process, frustration and anxiety rise among both patients and doctors. When controversy exists even among the

This work has been supported by the Lyme Disease Association of New Jersey and the Betz Family.

From the Department of Psychiatry, Columbia University Medical Center, and the Lyme Disease Research Program, New York, New York (BAF); private practice, Armonk, New York (JMK); Department of Medicine, Seton Hall University, and private practice, Basking Ridge, New Jersey (AG); and Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut (JAN)

leading academic researchers as to the validity and reliability of these tests, a battleground is then set in which doctors dispute amongst themselves over the diagnosis while the patient is left with an uncertain clinical syndrome in which treatment recommendations vary widely depending on the physician chosen. If this particular disease process also has psychiatric manifestations that lower the patient's frustration tolerance, increase irritability, and impair cognitive functioning, then the stage is set for a referral to a psychiatrist to address a presumed psychogenic or *functional* disorder. Such is the situation when dealing with Lyme disease. For example, in 1991, an essay appeared in a major medical journal entitled, *From the Centers for Fatigue Control (CFC) Weekly Report. Lime disease—United States*, in which patients with unexplained persistent fatigue were mocked for wondering whether or not they had Lyme disease, suggesting that they were clinging to a stylish diagnosis unable to accept that they actually suffered from a fictitious "Lime Disease."[14] This sarcastic essay resulted perhaps from a sense that the medical scientific community had full knowledge about this disease. Such was (and is) clearly not the case. The observation that fatigue after Lyme disease is a significant problem, that many of these patients would meet clinical criteria for chronic fatigue syndrome (CFS), and that a substantial portion of these patients appear to have signs in experimental CSF studies of persistent infection with *B. burgdorferi* has led the National Institute of Health to fund major research studies investigating the extent to which ongoing symptoms are due to persistent infection versus a "post-Lyme" syndrome.

Overdiagnosis of Lyme disease has been reported in rheumatology clinics. In 1990, a report[20] summarizing a chart review of 100 patients referred to a New Jersey Lyme Clinic indicated that only 25% had a history explicitly suggestive of Lyme disease. The most common other diagnosis was fibromyalgia. In 1993, an article[21] describing a retrospective case survey of 788 patients referred to another Lyme disease center revealed that only a minority (23%) of the patients met diagnostic criteria for active Lyme disease. An additional 20% of the 788 patients had confirmed previous Lyme disease with concurrent or residual symptoms and an additional 45% of the patients who were determined not to have ever had Lyme disease had negative serologic results in the authors' laboratory, but had had positive serologic results in other laboratories. Patients with fibromyalgia or CFS constituted the majority of cases of presumed misdiagnosis. Given that the symptoms of fatigue, myalgia, arthalgia, sleep disturbance, and persistent headaches are common during active Lyme disease and that both CFS and fibromyalgia are thought by some researchers to be triggered and perhaps perpetuated by infectious agents, excluding CFS and fibromyalgia as aspects of the syndrome of active Lyme disease seems premature in the history of our understanding of this illness.

Data to support the clinical speculation that many persistently symptomatic Lyme disease patients have one disease process and not multiple concomitant diseases was provided in 1994 by the results of a case-controlled community epidemiologic study.[19] Compared to controls, patients with a history of previously treated well-defined Lyme disease had significantly increased frequency of fatigue, arthralgias, paresthesias, poor coordination, inattention, emotional lability, and sleep disturbances. Less than half of these patients at follow-up were seropositive for Lyme disease. Among the 10 persistently symptomatic patients who were retreated, five improved. Although not a placebo-controlled study, the latter finding suggests that neuropsychiatric symptoms may persist in some patients despite prior therapy and that retreatment with antibiotics may result in further gains.

Possible misdiagnosis of Lyme disease and failure to identify another concurrent disease need to be considered seriously among patients who do not have a typical profile, whose tests are equivocal, or who are not responding to antibiotic treatment. In certain Lyme endemic areas, for example, approximately 10% of patients with Lyme disease may be coinfected with babesiosis, a comorbid infection which worsens the course of Lyme disease resulting in more frequent symptoms (fatigue, headaches, sweats, chills, anorexia, emotional lability, nausea) and a longer duration of illness.[13] Patients with major depression alone may have prominent fatigue, anorexia, emotional lability, myalgias, and insomnia, all symptoms that overlap with Lyme disease but by themselves do not make the diagnosis. Because a medical diagnosis is more socially acceptable, disabling major depression may go untreated for years. One patient, who consulted with one of the authors, with a prior history of Lyme disease was given long courses of antibiotic treatment for a constellation of symptoms, among which were prominent panic attacks and agoraphobia. After treatment with pharmacotherapy and behavior therapy, her panic attacks and medical condition dramatically improved. Although panic attacks and severe anxiety may be a symptom of untreated Lyme disease, when the Lyme disease has been treated but the anxiety persists physicians should suspect that an underlying Lyme-triggered or unrelated-but-concomitant psychiatric disorder exists.

Underdiagnosis of Lyme disease, however, is also a problem, particularly when the symptoms are primarily neuropsychiatric. In a survey of 193 patients with seropositive chronic Lyme disease,[7] patients reported having been sick for approximately 1 year and having had to consult with a mean of two doctors before the diagnosis of Lyme disease was made. Prior to diagnosis, 42.5% of these seropositive patients were thought to have had only a psychiatric disorder. Although this survey sample undoubtedly included some seropositive patients who may not have had Lyme disease, the results do suggest that neuropsychiatric problems are common in chronic Lyme disease, and that mental health professionals can play a critical role in the initial diagnosis.

In this article, the authors describe the typical clinical profile of Lyme disease and the tests that exist to support the diagnosis. They conclude with case studies of three patients who were initially thought to have other diagnoses: attention deficit disorder (ADD), depression, and multiple sclerosis (MS).

CLINICAL MANIFESTATIONS

In the early phase of infection after being bitten by an infected ixodes scapularis tick, common signs and symptoms include an erythematous annular rash (erythema migrans) followed by mild to severe flu-like symptoms. Hematogenous dissemination of the spirochete can occur within days to weeks of the tick bite. The organism may then lodge within the heart, eyes, joints, muscles, or central and peripheral nervous system. Although manifestations of target organ involvement may occur early, *B. burgdorferi* may remain quiescent for months to years before producing symptoms. Because of the potentially long latency period before disease onset, the fact that approximately one third of patients do not recall the tick-bite or rash, and the nonspecific nature of the early flu-like syndrome, infection by *B. burgdorferi* may not be recognized until long after the initial tick bite.

Approximately 15% to 40% of patients with Lyme disease develop neurologic problems.[4] Initially patients may complain of a bad headache without any signs of inflammation in the CSF. Early neurologic Lyme disease may be manifest

thereafter by meningitis, encephalitis, cranial neuritis, and motor or sensory radiculitis. Patients with meningitis often complain of a headache and stiff neck while the patients with encephalitis may have mood lability, irritability, confusional states, and poor sleep. Involvement of the seventh cranial nerve should automatically lead the clinician to test for Lyme disease, however only 5% to 10% of patients with neurologic Lyme disease have a Bell's palsy. Peripheral neuropathies (motor or sensory) may result in sharp shooting or stabbing pains, burning pains, paresthesias, weakness, or fasciculations. Later stage neurologic Lyme disease may result in a chronic encephalopathy (see below) or an encephalomyelitis. Encephalomyelitis, markedly less common, may be characterized by spastic paraparesis, transverse myelitis, cerebellar syndromes, hemiparesis, or movement disorders. Rarely patients with neurologic Lyme disease may have strokes, seizures, or severe dementia.

Lyme encephalopathy is characterized by subtle to severe disturbances in cognition, affecting primarily short-term memory, verbal fluency, attention and concentration, and processing speed. Patients may complain that their brains are "in a fog" or that their reaction time is slower. Recitation of their history may be very disorganized because these patients have a hard time keeping track of their thoughts. Some of these patients are so distractible that they may appear to have new-onset attention deficit disorder. Although memory storage is often not impaired, patients may have a hard time retrieving information. Word transpositions are not uncommon, such that a patient might say, "I put the microwave in the dinner" instead of "I put the dinner in the microwave." Other concomitant symptoms associated with late Lyme disease include profound fatigue, sleep disturbance, photophobia, hyperacusis, periods of geographic disorientation, and disturbances of mood.

The plethora of psychiatric problems associated with Lyme disease were first reviewed in 1990 in the European medical literature by Drs. Kohler[12] and Omasits.[17] Kohler attempted to categorize the psychiatric symptoms by stage, listing depressive mood in early disease, organic personality disorders in mid-stage disease, and organic psychoses, dementia, and anorexia in the later phase of the illness. Omasits stated that psychiatric manifestations can be predominant and that the clinical spectrum of Lyme disease ranges from agitated depressive states with suicidal ideas to the clinical picture of dementia. A review of the medical literature[8] revealed that, in addition to the disorders listed by Kohler and Omasits, Lyme disease appear to be capable of causing syndromes which manifest as personality change, depersonalization, mania, hallucinations (auditory, visual, and olfactory), paranoia, catatonia with stupor and mutism, somatization disorder, obsessive compulsive disorder, violent outbursts, panic attacks, and disorientation.

In children and adolescents with neurologic Lyme disease, behavioral or mood disturbances are the second most frequently reported symptom.[1] Common neuropsychiatric symptoms include headaches, fatigue, difficulty with concentration in school, irritability, oppositional behavior, and new onset anxiety disorders. When the onset of illness is not dramatic, but characterized by gradually increasing fatigue, disinterest, and inattention, children may begin to label themselves as incompetent as they realize they can no longer keep up with the rest of their classmates academically. While developmental and family issues always need to be considered when there is a change in a child's behavior or mood, in endemic areas Lyme disease should be considered as well, particularly because delays in diagnosis are associated with greater chronicity.

DIAGNOSTIC TOOLS

When Lyme disease is suspected clinically, the clinician should order a Lyme ELISA and a Lyme Western Blot, both indirect serologic tests that detect the presence of antibodies against *B. burgdorferi*. Whereas the ELISA is a less expensive screening test, it is less specific (and perhaps less sensitive) than the Western blot, resulting in false positives among patients infected with other spirochetal conditions, such as syphilis or periodontal disease. Because patients can have a negative ELISA but a positive Western blot, polymerase chain reaction (PCR) assay, or culture, and both an ELISA and Western blot should be ordered.[11, 16] The test should be sent to a laboratory with established reliability in conducting Lyme assays. The Centers for Disease Control (CDC) guidelines currently used by many commercial laboratories for the interpretation of the Western blot are overly restrictive in that patients with active Lyme disease may not have the requisite 5 of 10 specific bands. In addition, certain bands not listed as specific such as the 31 Kd (Osp A) and 34 kD (Osp B) bands are in fact highly specific, the former being used to create the new Lyme vaccines. Other tests that may be helpful include more direct tests such as the PCR assay that detects the presence of the DNA of the spirochete and antigen detection assays (in urine or cerebrospinal fluid [CSF]) which detect pieces of the spirochete itself. These tests are stronger indications that the organism may in fact be present; however, they do not necessarily indicate that the spirochete is alive. The best and most definitive test is based on culture, although this test has a very low yield in late Lyme disease.

Overutilization of Lyme serologic tests can lead to a higher likelihood of false positive results. When tests are used as an indiscriminate screen, ordered without regard for clinical presentation, risk factors, and history, one report indicates that the positive predictive value of a test falls to 7%.[10] When tests are ordered for patients with a typical clinical history of Lyme disease, the positive predictive value rises to over 96%. The clinical history therefore is extremely important.

A recent FDA Public Health Advisory statement[3] on assays for Lyme disease warned: "A positive result does not necessarily indicate current infection with *B. burgdorferi*, and patients with active Lyme disease may have a negative test result." For example, in early Lyme disease with erythema migrans, patients are expected to have negative serologies because detectable levels of borrelia-specific antibodies have not yet been produced. In later chronic Lyme disease, among patients who were treated early in their illness, negative or equivocal serologies may result presumably because the early antibiotic treatment abrogated the immune response. In one recent study,[13] of 8 patients with late Lyme encephalopathy who had CSF evidence of active central nervous system (CNS) infection, half of the patients had equivocal serologic results and one quarter were seronegative. This study, in addition to demonstrating the presence of seronegative Lyme disease, points out the importance of spinal fluid assays among patients with suspected central nervous system involvement.

Other tests that are a key part of the evaluation include neuropsychologic testing, CSF studies, and structural and functional imaging. Neuropsychologic tests of memory, attention, processing speed, and verbal fluency can detect objective evidence of cognitive dysfunction that may not be immediately observable on clinical exam. The most common problems are in memory retrieval and attention. CSF tests in early neurologic Lyme disease may demonstrate intrathecal antibody production, although in later Lyme disease the results of CSF antibody studies may be negative up to 43% of the time.[5] More commonly the CSF may reveal a mild increase in protein or a pleocytosis. Because a normal

CSF may be seen in 20% of patients with active central nervous system infection with *B. burgdorferi*, this test cannot be used to exclude the diagnosis of Lyme disease. MRI scans may reveal T2 weighted white matter hyperintensities similar to the demyelinating lesions associated with MS. Functional imaging may reveal a diffuse pattern of heterogeneous uptake, resembling patients with vasculitides.[9, 15] In late neurologic Lyme disease, SPECT and PET imaging appear to be more sensitive in detecting objective abnormalities than MRI scans. Neuropsychiatrists therefore may find functional imaging particularly helpful in the effort to tease out whether a patient's problems are primarily psychiatric or owing to another more diffuse central nervous system process.

ILLUSTRATIVE CASES

Three cases are presented below, one child, one adolescent, and one adult. Each demonstrates the complexity of presentation, diagnosis, and course.

Case Study 1
Attention Deficit Disorder Versus Lyme Disease

At age 7, Susan who lived in a Lyme endemic area developed problems focusing in school. A neuropsychologist diagnosed probable ADD. Other symptoms included lethargy, irritability, forgetfulness, headaches, poor coordination, joint pain, word-finding difficulties, and light and sound sensitivity. A comprehensive medical work-up, including EEG and MRI, were within normal limits, except for a positive Lyme ELISA. Once Lyme disease was diagnosed and treated, her symptoms of attention deficit disorder resolved and her school grades returned to their pre-Lyme disease level of excellence. Her course over the subsequent 2 years appeared to be antibiotic-dependent, such that she would do well as long as she stayed on antibiotics and relapse when taken off. At age 9, she was able to come off antibiotics and remained symptom free for 3 years, performing in the A/A+ range academically. Knee pain, frequent headaches, and poor concentration re-emerged at age 12. Serologic tests revealed a positive ELISA with fully reactive IgG and IgM Western blots. A brain SPECT revealed normal perfusion. Treatment with oral cefuroxime for 2 months led to a rapid improvement in all symptoms, however within 2 weeks of stopping antibiotics her symptoms returned. During the following months, her teachers recorded a variety of problems: "trouble with consistency in day-to-day work; careless; head in the clouds; scattered and sloppy work; assignments are late, forgotten, or lost; difficult time following directions; more forgetful and disorganized." Her parents noted that Susan would go to school with homework in her bag but once there have no idea where it was or whether she had done it. Emotionally, she had become frustrated, overwhelmed, tearful, aggressive, and fearful with new onset phobias and nightmares. Physically, she had knee pain with mild swelling, paresthesias, headaches, moderate fatigue, insomnia, and trouble focusing.

On mental status examination, Susan acknowledged having problems in 6 of the 9 inattention areas identified in the DSM-IV criteria for attention deficit hyperactivity disorder (ADHD), thereby qualifying for the diagnosis. She denied significant depression or suicidal feelings but acknowledged feeling overwhelmed. Cognitive testing after being off of antibiotics for 4 months revealed that she had a very superior baseline intelligence (verbal IQ 132) but significant deficits in visual motor planning, speed of processing, visual scanning, attention, visual memory, and learning. She was diagnosed then as having a persistent encephalopathy secondary to Lyme disease and treated with additional oral antibiotics. She continues on oral cefuroxime several months later and has had a full return to her prior level of health and academic excellence, with no evidence of the prior ADHD symptoms.

Case Study 2
Depression Versus Lyme Disease

David, a 16-year-old boy who lived in a Lyme endemic area, presented complaining of long-standing depression, exacerbated recently when he stopped dating a girl after only 2 weeks because he felt too tired and not smart enough. He reported anger, frustration, insomnia, poor appetite, mild weight loss, and passive suicidal ideation: "I wish I could just die in my sleep." He was oriented to person and place, but when asked the date he said 1977 instead of 1997. He reported feeling spaced out all the time, as if in a fog.

David's recent medical history was notable for painful knees throughout much of 7th grade, such that he had to quit sports. A previous A/A− student, his grades declined to Bs. He appeared lazy because he found it hard to get out of bed in the morning and often forgot to hand in assignments that he had in fact completed. His grades declined during 8th and 9th grades such that by 10th grade he was nearly failing most of his courses. The presumed cause of his poor performance was either laziness or mild depression. When asked about his school difficulties, he reported trouble staying awake in class and trouble concentrating. When asked about his physical and cognitive status, he acknowledged severe headaches; facial fasciculations; myalgias; stiff neck; hyperacusis; episodic paresthesias of his face and hands; sudden sweating; painful joints; sore throats; palpitations; electric shock-like pains; word-finding problems such that it was hard to finish sentences; semantic paraphasias; short-term memory problems such that he could not recall conversations; and testicular pain. David had had embedded tick bites, but he could not recall ever having had an erythema migrans rash.

Given the suspicious clinical history, further testing was done. Although a Lyme ELISA was negative twice in the prior 3 months, his IgG Western blot revealed 4 of the 5 requisite CDC specific bands. Other tests, including TFTs, heterophile antibodies, and brain MRI with FLAIR sequences were unremarkable. Neuropsychologic testing revealed significant deficits in processing speed and visual spatial memory, in a young man whose premorbid intellectual capacity was estimated to be in the 85th percentile. A brain SPECT was ordered that revealed moderate to severe diffusely and heterogeneously decreased perfusion in the cortex and the central white matter, consistent with encephalitis, vasculitis, and Lyme disease. Based on these findings, a diagnosis of probable Lyme encephalopathy was made and he was treated with 12 weeks of IV ceftriaxone with excellent results physically (sleep, appetite, headaches, joint pains, distractibility, numbness), cognitively (distractibility, short-term memory), and emotionally. Anti-depressant medications had been recommended prior to IV treatment, but were not taken. The patient was no longer depressed after the IV antibiotic regimen and his school performance markedly improved. David's follow-up neuropsychologic testing revealed an improvement of 22 full-scale IQ points.

Case Study 3
Multiple Sclerosis Versus Lyme Disease

Mr. B, a 45-year-old research scientist recently diagnosed as having MS, presented asking whether any of his current symptoms might be related to a

diagnosis of Lyme disease 6 years earlier. Current symptoms included headaches, arthritis, sleeping difficulties, paresthesias, tremors, fasciculations, irritability, visual problems, and short-term memory difficulties.

At age 39, shortly after two tick bites from a Lyme endemic area, the patient experienced a severe flu and myalgias, followed by marked headaches, fatigue, leg weakness, migratory lower extremity polyarthritis, paresthesias, loss of touch, and temperature sensation below the hips, and urinary sphincter dysfunction. Serologic tests were unremarkable, including a Lyme ELISA and rheumatoid factor. Although some CSF studies (including VDRL, Lyme titers, and oligoclonal bands) were within normal limits or nonreactive, he did have a pleocytosis of 7 white blood cell (WBC) count and mildly elevated myelin basic protein. A neurologist diagnosed transverse myelitis, secondary to presumed seronegative Lyme disease. He was treated with intramuscular ceftriaxone for 2 weeks followed by 4 weeks of oral doxycycline with resolution of his headaches. This was followed by oral prednisone with resolution of his leg weakness and foot drag. Although markedly improved, over the subsequent 5 years he was intermittently symptomatic with ankle pain, headaches, night sweats, fasciculations, paresthesias below the waist, insomnia, and testicular pain. The cause of these persistent symptoms was unclear.

At age 44, his symptom profile worsened: more severe headaches, slurred speech, left facial and upper extremity tingling, double-vision, poor coordination with poor postural balance, and lightheadedness. Neurologic examination revealed dysarthric speech, decreased pain, and temperature sensation and a delayed corneal reflex on the left side of his face, decreased temperature sensation in the lower extremities, and a markedly abnormal cerebellar examination. A brain MRI revealed multiple areas of focal white matter disease extending from the brain stem to the parieto-occipital lobe. Median nerve somatosensory evoked potential studies were within normal limits. Visual evoked potential studies were abnormal suggestive of optic nerve or severe retinal disease on the left and axonal optic nerve dysfunction on the right. CSF was within normal limits with no evidence of Lyme antibodies, oligoclonal bands, or elevated myelin basic protein. Despite the normal CSF, he was diagnosed clinically as having probable MS. After treatment with prednisone, he experienced improved energy and vision, but continued to have diffuse multisystemic symptoms.

Now at age 45, he presented with the symptoms identified above. Lyme serologies revealed a Western blot IgG that met full CDC criteria for reactivity. Other laboratory tests were within normal limits (including FTA, ANA, RF, ACE, anti-cardiolipin antibody) except for a mild polyclonal increase of IgM. Brain SPECT revealed decreased perfusion diffusely throughout the cortex, the white matter, and the basal ganglia bilaterally. The diagnosis of Lyme disease was made, although concurrent MS could not be excluded.

Over the subsequent 9 months, off all steroids, Mr. B was treated with high dosages of oral cefuroxime and minocycline. Although improvement occurred in all symptoms such that he was able to return to work, a return of left-sided paresthesias and weakness led to a repeat MRI which showed a worsening of demyelination in the brainstem. He was then started on a regimen of intravenous ceftriaxone (2 g IV qd) and clarithromycin (500 mg po BID), both of which he continues on now 12 months later. Since the IV antibiotics were started, serial MRI scans at the same center revealed progressive diminution in the size of all white matter lesions and the development of no new lesions. Based on the history, Lyme serologies, and antibiotic responsiveness, both his neurologist and infectious disease doctors changed their diagnosis from MS to a resolving antibiotic responsive Lyme encephalomyelitis.

Discussion

These three cases demonstrate that patients with Lyme disease may have variable neuropsychiatric presentations, equivocal or negative serologic test results, incomplete treatment response and subsequent relapses. As is true for most patients with neuropsychiatric Lyme disease, each of these patients had a history of multisystemic symptoms after exposure to a Lyme endemic area. In the absence of such a history, Lyme disease is not likely to be the correct diagnosis.

Inattention and poor mental tracking are common features of Lyme encephalopathy in both children and adults. Although impulsivity and hyperactivity may be seen, more often children with Lyme-induced ADHD meet criteria for only the inattention subtype. The initial treatment should be antibiotics, followed later by psychopharmacologic approaches to help diminish any residual problems with inattention.

The optimal duration of antibiotic treatment in chronic Lyme disease is unknown, although typically patients are initially given 4 to 6 weeks followed by longer courses if relapse occurs.[2, 6, 13a] In case 1, Susan appeared to need long courses of oral antibiotics to remain symptom free. An understanding of the microbiology of this spirochete sheds light on why Lyme disease may require longer courses of treatment. *Borrelia burgdorferi* has many features that are typical of organisms that are difficult to eradicate: a slow rate of growth; ability to remain dormant for long periods; intracellular invasion; and, sequestration in areas where antibiotic penetration is more difficult, such as the central nervous system or the anterior chamber of the eye. Case study 2 demonstrated that even among patients who have had Lyme disease undetected for long periods, antibiotic treatment can be helpful although perhaps not curative.

The depression associated with the earlier encephalitic phase of neurologic Lyme disease is characterized by marked irritability and mood lability. Later, in the setting of encephalopathy, the depression is often more mild, characterized primarily by anhedonia, low energy, hopelessness regarding the future, and a diminished sex drive. In case study 2, David's long-standing depressive state appeared to be a chronic dysthymia. The diagnosis of Lyme disease would have been missed had the physician not asked explicitly about specific cognitive and physical symptoms. After the initiation of antibiotic treatment, he had to be carefully educated about the fact that he had been suffering from an undiagnosed infectious illness over the last few years that had been draining his energy. Rather than being lazy and incompetent, he had been sick. With this new understanding, David was able to perceive himself in a new way and once again apply himself to his studies, working hard to make up for the years of illness.

Differentiating Lyme encephalomyelitis from MS can be difficult. Mr. B in case study 3 had many of the clinical features of MS, including double vision, optic neuritis, paresthesias in one half of the body, disturbed micturition initially, cerebellar involvement, and diffuse white matter disease. Mr. B's CSF however did not have the characteristic oligoclonal bands which are seen in over 90% of patients with MS but in fewer than 5% of patients with neurologic Lyme disease. Nor did his CSF demonstrate the common finding in MS of a marked elevation in myelin basic protein. The negative CSF results for MS, the positive serologic tests for Lyme disease, clinical improvement with antibiotics, and progressive diminution of MRI hyperintensities together confirmed the diagnosis of Lyme encephalomyelitis.

Although none of the three patients in this report took psychiatric medications, psychopharmacology can be very valuable adjunctively for patients deal-

ing with persistent or severe neuropsychiatric symptoms. For example, carbamazepine may help to reduce paroxysmal pain or hyperacusis. Bupropion may help to diminish depression and enhance attention.

In conclusion, in endemic areas, although Lyme disease may be an overdiagnosed disorder in rheumatology clinics, it may be an underdiagnosed disorder in child and adults psychiatry clinics. Although none of the currently available tests for Lyme disease other than direct culture definitively indicates active infection, the clinical presentation and the multiplicity of tests taken together can serve as guideposts for the clinician.

References

1. Belman AL, Iyer M, Coyle PK, et al: Neurologic manifestations in children with North American Lyme Disease. Neurology 43:2609–2614, 1993
2. Burrascano JJ: Lyme disease. *In* Conn's Current Therapy. Philadelphia, WB Saunders Company, 1997, pp 140–143
3. Burlington DB: FDA Public Health Advisory: Assays for Antibodies to Borrelia burgdorferi: Limitations, Use, and Interpretation for Supporting a Clinical Diagnosis of Lyme Disease. Department of Health and Human Services, United States Public Health Service, Food and Drug Administration, July, 1997
4. Coyle PK: Neurologic Lyme Disease. Semin Neurol 12:200–208, 1992
5. Coyle PK, Schutzer SE, Deng Z, et al: Detection of Borrelia burgdorferi-specific antigen in antibody-negative cerebrospinal fluid in neurologic Lyme disease. Neurology 45:2010–2015, 1995
6. Donta ST: Tetracycline therapy for chronic Lyme disease. Clin Infect Dis 25(suppl 1):S52–S56, 1997
7. Fallon BA, Nields JA, DelBene D, et al: Depression and Lyme disease: A controlled survey (abstract #NR119). *In* New Research Program and Abstracts of the 144th Annual Meeting of the American Psychiatric Association. Washington, DC, American Psychiatric Association, 1991, p 76
8. Fallon BA, Nields J: Lyme disease: A neuropsychiatric illness. Am J Psychiatry 151:1571–1583, 1994
9. Fallon BA, Das S, Plutchok J, et al: Functional imaging neuropsychological testing in Lyme disease. Clinical Infectious Diseases 25:S57–S63, 1997
10. Golightly MG: Laboratory consideration in the diagnosis and management of Lyme borreliosis. AJCP 99:168–174, 1993
11. Kochevar JM, Liegner K: Simultaneous ELISA and Western Blot Testing in Evaluation of Patients for Suspected Lyme Disease (research abstract). Tenth Annual International Scientific Conference on Lyme Borreliosis and other Tick-Borne Disorders. Bethesda, MD, National Institute of Health, 1997
12. Kohler VJ: Lyme disease in neurology and psychiatry. Fortschr Med 108:191–194, 1990
13. Krause PJ, Telford SR, Spielman A, et al: Concurrent Lyme disease and babesiosis: Evidence for increased severity and duration of illness. JAMA 275:1657–1660, 1996

13a. Liegner KB, Duray P, Agricola M, et al: Lyme disease and the clinical spectrum of antibiotic-responsive meningoencephalomyelitides. J Spirochetal and Tick Borne Diseases, in press

14. Lettau LA: From the centers for fatigue control (CFC) weekly report: Lime disease—United States. Ann Intern Med 114:602, 1991
15. Logigian EL, Johnson KA, Kijewski MF, et al: Reversible cerebral hypoperfusion in Lyme encephalopathy. Neurology 49:1661–1670, 1997
16. Oksi J, Uksila J, Marjam AM, et al: Antibodies against whole sonicated Borrelia burgdorferi spirochetes, 41-kD flagellin and P39 protein in patients with PCR- or culture-proven late Lyme borreliosis. J Clin Microbiol 33:2260–2264, 1995
17. Omasits M, Seiser A, Brainin M: Recurrent and relapsing borreliosis of the nervous system. Wien Klin Wochenschr 102:4–12, 1990

18. Pachner AR: Neurologic manifestations of Lyme disease, the new "Great Imitator." Rev Infect Dis 11(suppl 6):S1482–S1486, 1989
19. Sigal LH: Summary of the first 100 patients seen at a Lyme disease referral center. The Am J Med 88:577–581, 1990
20. Shadick NA, Phillips CB, Logigian EL, et al: The long-term clinical outcomes of Lyme disease. Ann Intern Med 1221:560–567, 1994
21. Steere AC, Taylor E, McHugh GL, et al: The overdiagnosis of Lyme disease. JAMA 269:1812–1816, 1993

Address reprint requests to

Brian A. Fallon, MD, MPH
The NYS Psychiatric Institute
Lyme Disease Research Program
722 West 168th Street, #13
New York, NY 10032