The Underdiagnosis of NeuroPsychiatric Lyme Disease in Children and Adults

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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. 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

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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 Insect Control (CICO) Weekly Report, Lyme 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 unstable to accept that they actually suffered from a fictitious "Lyme Disease." 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 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 describing a retrospective case survey of 788 patients referred to another Lyme disease center revealed that only a minority (33%) 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 40% 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. 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 neuro-psychiatric 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 con-
current disease need be considered seriously among patients who do not have a typical profile, whose tests are equivocal, or who are not responding to antipsychotic medicines. In certain Lyme endemic areas, for example, approximately 30% of patients with Lyme disease may be treated with a combination of antibiotics, a neurocardioid infection which worsens the course of Lyme disease resulting in more frequent symptoms (fatigue, headache, nausea, chills, fever, emotional lability, anxiety) and a longer duration of illness.1 Patients with major depression alone may have prominent fatigue, anxiety, 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 con- sulted with me of the authors, with a prior history of Lyme disease was given long courses of antidepressant 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, which the Lyme disease has been treated but the anxiety persists, physicians should suspect that an underlying Lyme- triggered panic disorder or coexisting panic disorder exists.

Understanding of Lyme disease, however, is also a problem, particularly when the symptoms are primarily neuropsychiatric. In a survey of 143 patients with seropositive chronic Lyme disease,2 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, 62.5% 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 mood and mood disorders 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 medical attention deficit disorder (ADD), depression, and multiple sclerosis (MS).

CLINICAL MANIFESTATIONS

In the early phase of infection after being bitten by an infected host, acral papules or ulcers occur on the skin. In addition, we have seen several patients who have also had a localized skin reaction at the site of the tick bite. The organism may then lodge within the heart, eye, joints, muscles, or central and peripheral nerves. Although manifestations of target organ involvement may occur early, B. burgdorferi may remain quiescent for months to years before producing symptoms. Because of the potential for latent period between the tick bite and the disease onset, it is not unlikely that many patients do not recall the tick bite or rash, and the nonspecific nature of the early flu-like symptoms can be self-diagnosed. B. burgdorferi, however, may be present for a year or more before the initial tick bite. Approximately 15% to 40% of patients with Lyme disease develop neurologic problems. Initially patients may complain of a head or body without any signs of inflammation in the CNS. Early neurologic Lyme disease may be manifested
thereafter by encephalitis, encephalopathy, cranial nerves, and motor or sensory impairments. Patients with meningitis often complain of headache and stiff neck, while the patients with encephalitis may have mood lability, irritability, confusion, 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. Symptomatic nervous system manifestations (sensation or memory) may result in severe weakness, atrophic pains, burning pains, numbness, weakness, or sensory changes. Later stage neurologic Lyme disease may result in a chronic encephalopathy (see below) or encephalomyelitis. Cerebellar ataxia, memory loss, can be characterized by spastic paraparesis, transverse myelitis, cortical syndromes, hallucinations, or movement disorders. Rarely patients with neurologic Lyme disease may have stroke, 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 increasing sleep. Patients often complain that their brains are "in a fog" or that their reaction time is slower. Recollection 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 appear to have new-onset attention deficit disorder. Although memory loss is often not impaired, patients may have a hard time retaining information. Word substitutions are not uncommon, such that a patient might say, "I put the instructions in the drawer" instead of "I put the drawer in the instructions." Other concurrent 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 1993 in the European medical literature by Des. Kohler and Omens. Kohler attempted to categorize these psychiatric symptoms by stage, listing depressive mood in early disease, organic personality disorders in midstage disease, and affective psychosis, dementia, and anosmia in the later phase of the illness. Omens stated that psychiatric manifestations can be profound but that the clinical spectrum of Lyme disease ranges from agitated depressive states with suicidal ideation to the clinical picture of dementia. A review of the medical literature revealed that in addition to the disorders listed by Kohler and Omens, Lyme disease appear to be capable of causing syndromes which manifest as personality change, depersonalization, mania, hallucinations (hallucinations of sound, visual, and olfactory), paranoia, catatonia, stupor and mutism, somnolence, obsessive compulsive disorder, violent outbursts, panic attacks, and dissimulation.

In children and adolescents with neurologic Lyme disease, behavioral or mood disturbances are the second most frequently reported symptom. Common neuropsychiatric symptoms include headache, fatigue, difficulty with concentration, in school, inattentive, oppositional behavior, and new onset ANSWER.....
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 specific 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 of cerebrospinal fluid (CSF) should be undertaken. 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 3 of 10 specific bands. In addition, certain bands do not ladder as specific as the 31 Kd (Cap A) and 54 Kd (Cap B) bands. Hence, in this context, the term "positive Western blot" is in fact highly specific, the former being used to create the new Lyme vaccines. Other tests that may be helpful include some 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 not available in many areas. The term "positive Western blot" is the best and most definitive test to be used on a consistent basis, although this test has a very low yield in the Lyme disease.

Overutilization of Lyme serologic tests can lead to a higher likelihood of false positive results. When tests are used in an indiscriminate manner, ordered without regard for clinical presentation, risk factors, and history, one report indicates that the positive predictive value of a test falls to 75%. When tests are ordered for patients with a typical clinical history of Lyme disease, the positive predictive value rises to over 90%. The clinical history therefore is extremely important.

A recent FDA Public Health Advisory statement 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 serologic tests. Detectable levels of borrelia-specific antibodies have not yet been produced. In late chronic Lyme disease, among patients who were treated early in their illness, negative or equivocal serologies may result possibly because the early antibiotic treatment abrogated the immune response. In one recent study, 1 of 82 patients with late Lyme erythema migrans who had CSF evidence of active central nervous system (CNS) infection, half of the patients had equivocal serologic results, and 1 of 24 patients were seronegative. This study, in addition to demonstrating the presence of seroconverting Lyme disease patients, points to 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 neurophysiologic testing, CSF studies, and structural and functional imaging. Neurophysiologic tests of memory, attention, processing speed, and verbal fluency can detect abnormalities indicative of cognitive dysfunction. If these abnormalities are not demonstrated directly on clinical exam, then the most common problems are in sensory retrieval and American. CSF tests in early neuroradiologic Lyme disease may demonstrate intrathecal antibody production, although in later Lyme disease the results of CSF antibody studies may be negative up to 40% of the time. More commonly the CSF may reveal a mild increase in protein or a pleocytosis. Because a normal
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 ceftriaxone several months later and has had a full return to her prior level of health and academic excellence, with no evidence of the prior ADIE syndrome.

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 B’s. 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; myalgia; stiff neck; hypersomnia; 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 specificities. Other tests, including TFRs, 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 diffuse 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 encephalitis was made and he was treated with 32 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,
Discussion

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

Inattention and motor 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 ADD/ADHD meet criteria for only the inattention subtype. The initial treatment should be antibiotics, followed by psychopharmacological 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 usually given 4 to 6 weeks followed by longer courses if relapse occurs. In case 1, Susan appeared to need long courses of oral antibiotics to remain symptom-free. An understanding of the microbiology of this infection 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 had had Lyme disease underdosed for long periods, antibiotic treatment can be helpful although perhaps not curative.

The depression associated with the earlier encephalopathic phase of neuropsychiatric Lyme disease is characterized by marked irritability and mood lability. Later, in the setting of encephalopathy, the depression is often more severe, characterized primarily by asthenia, low energy, hypotension 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 irresponsible, 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.

Delirium, dysthymia, and neuropsychiatric symptoms from MS can be difficult. Ms. B. In case study 3 had many of the clinical features of MS, including double vision, optic neuritis, paraparesis in one half of the body, Disturbed Michaelson's box, cerebellar involvement, and diffuse white matter disease. Ms. B's CSF however did not have the characteristic oligoclonal bands which are seen in over 80% of patients with MS. But in fewer than 3% of patients with neuropsychiatric Lyme disease. Nor did her 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 elimination of MS hyperintensities together confirmed the diagnosis of Lyme encephalopathy.

Although most of the three patients in this report took psychiatric medications, psychopharmacology can be very valuable adjunctively for patients dealing...
by with persistent or severe neuropsychiatric symptoms. For example, carbamazepine may help to reduce paroxysmal pain or hyperexcitability. Gabapentin may help to diminish depression and enhance attention.

In conclusion, in endemic areas, where Lyme disease may be an over-diagnosed disorder in rheumatology clinics, it may be an under-diagnosed disorder in adults with neuropsychiatric symptoms. 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 guidelines for the clinician.

References


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