

Lyme Disease, Comorbid Tick-Borne Diseases, and Neuropsychiatric Disorders

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Many recall the phrase "To know syphilis is to know medicine." Now Lyme disease (Lyme borreliosis), the new "great imitator,"¹ is the ultimate challenge to the breadth and depth of our knowledge. In psychiatry, we generally treat mental symptoms or syndromes rather than the underlying cause of a disorder. A greater awareness of immune reactions to infections and other contributors to mental illness enhances our psychiatric capabilities. Lyme disease, like syphilis, is caused by a spirochete with a multitude of possible manifestations and 3 stages: early with dermatological symptoms, disseminated, and late stage.

Unlike *Treponema pallidum*, the cause of syphilis, the causative agent of Lyme disease, *Borrelia burgdorferi*, can be much more difficult to eliminate, diagnostic testing is less reliable, and interactive copathogens are major contributors in the pathophysiology.^{2,3} *B burgdorferi* is highly adaptable with 6 times as many genes as *T pallidum* and 3 times as many plasmids as any other bacteria that allow rapid genetic adaptations.^{4,5} It is a stealth pathogen that can evade the immune system and pathophysiological mechanisms.^{6,7} Knowingly or not, most psychiatrists have at some point been perplexed by patients with late-stage psychiatric manifestations of Lyme borreliosis. Several factors are associated with the risk of infection as well as the different manifestations of Lyme borreliosis ([Table 1](#)).

Table 1 Factors associated with risk for Lyme disease and its associated manifestations		
Predisposing factors	Precipitating factors	Perpetuating factors
HLA DR2, HLA DR4 genotype	Tick bite (initial infection)	High bacterial load
Compromised immune system	Episode of acute stress (relapse)	Reinfections
Coinfections that cause immunosuppression	Immunosuppression (relapse)	Coinfections
Ecosystem that fosters tick-borne disease (infection)	Vaccination (relapse)	Chronic unremitting stress
Outdoor activities (infection)	Childbirth (relapse)	Sleep deprivation
	Auto accident (relapse)	Corticosteroid exposure
	Coinfection (relapse)	Misdiagnosis
		Undertreatment

A problematic case

The following composite case illustrates a number of problems that may make diagnosis and treatment of Lyme borreliosis anything but straightforward. The patient is in good health and enjoys outdoor activities. Often this person has the HLA DR4 genotype. He or she may acquire

a small tick bite that goes unnoticed because the subsequent rash may not be of the classic bull's-eye type, may be easily overlooked in dark-skinned individuals, may be misdiagnosed, or may occur only with a second or subsequent infection. There may be flu-like symptoms with migratory musculoskeletal aches and pains. If a diagnosis of Lyme disease is made, the initial course of antibiotic treatment may not have been sufficient to eliminate the infection. (Although standardized by 1 set of guidelines, psychiatrists often see the failures of some of the "standard" treatments.) Low-grade symptoms may remit and periodically relapse over time. An accident, emotional stress, vaccination, or childbirth can trigger an exacerbation of symptoms.

The patient, who did not have psychosomatic symptoms and was not hypochondriacal in the past, now complains of an increasing number of somatic, cognitive, neurological, and psychiatric symptoms. Although Lyme disease may be suspected, the laboratory tests available to most clinicians often lack sensitivity and thus are read as negative for Lyme disease. Fibromyalgia, chronic fatigue syndrome, or multiple sclerosis (MS) may be erroneously diagnosed.

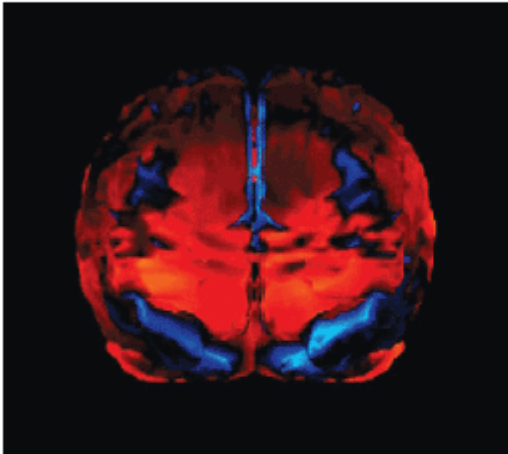
Treatment of some symptoms with corticosteroids may initially provide relief, but a more rapid decline often follows. The patient sees multiple specialists, each of whom restricts the examination to his area of expertise. Nothing is resolved, and the patient is frustrated that his symptoms cannot be explained. In view of the growing list of unexplained symptoms, including psychiatric symptoms, the patient is treated with tranquilizers and antidepressants with some benefit, but gradual decline persists.

The major complaints include fatigue, multiple cognitive impairments, depression, anxiety, irritability, head-aches, and a multitude of other symptoms. When general medical treatment fails, the patient may be referred to a psychiatrist for 3 reasons: the unexplained medical symptoms give the appearance of a psychosomatic or somatoform condition; complex mental symptoms are thought to require psychiatric assessment; and a psychiatrist is thought to be needed to more effectively manage psychiatric treatments.

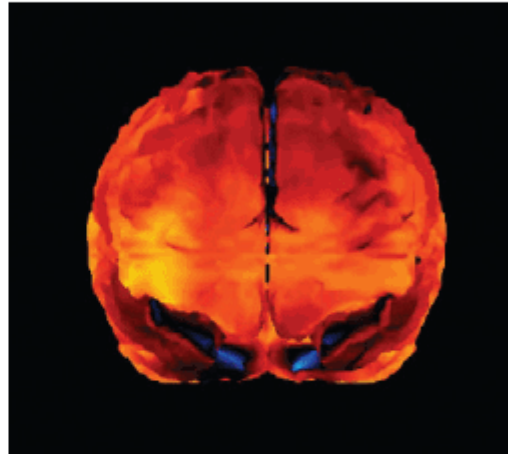
Figure

SPECT images of the brain before and after treatment with ceftriaxone

Before



After



Initial SPECT scan shows extensive hypoperfusion, predominantly in the frontal and temporal lobes and to a lesser degree in the parietal and occipital lobes. After treatment, there is marked improvement of the hypoperfusion pattern in the temporal, frontal, and parietal lobes; only small areas of the hypoperfusion pattern remain.

SPECT, single photon emission CT.

The [Figure](#) presents single photon emission CT (SPECT) images of the brain of a depressed 51-year-old woman with Lyme disease, before and after treatment with ceftriaxone. She walked on nature trails at home and on vacations, recalled frequent tick bites and an expanding bull's-eye rash on her abdomen with no other symptoms, but considered it of no special significance at the time. Over 8 years, there was a progressive development of unexplained symptoms that began with GI complaints, followed by cognitive impairment, fatigue, depression, arthritis, and shortness of breath. The primary diagnosis was atypical depression. Although the patient failed to respond to 51 different drug trials, the treating psychopharmacologist assured her the mental symptoms could not possibly be caused by an underlying physical condition.

The initial SPECT scan demonstrated "extensive hypoperfusion... predominantly in the frontal and temporal lobes and to a less degree in the parietal and occipital lobes," which is consistent with Lyme disease and neurodysfunction. Neurocognitive testing demonstrated significant abnormalities. An MRI scan ruled out frontal temporal dementia. The patient tested negative for Lyme disease by CDC epidemiological criteria, but the Lyme IgG Western blot test result was positive at one laboratory and equivocal at another. The CD57 lymphocyte count was low at 17/ μ L (60 to 360) and the patient tested positive for 4 other tick-borne infections (*Mycoplasma fermentans*, *Babesia microti*, *Babesia WA-1*, and *Bartonella henselae*). The patient was intolerant to oral antibiotics and was treated with 8 months of intravenous ceftriaxone. The second SPECT scan demonstrated "marked improvement of the hypoperfusion pattern in the temporal, frontal, and parietal lobes and small areas of hypoperfusion pattern remain." The depression never returned, but some mild residual symptoms persist, including fatigue, neuropathy, and arthritis; however, she has mostly returned to her active lifestyle. The failure to diagnose and treat these infections for several years resulted in an escalation of

symptoms and a loss 8 years of her life that could have been prevented by earlier diagnosis and treatment.

General theoretical issues

The causes of most psychiatric illnesses are unknown. The catecholamine hypothesis does not adequately explain the cause of abnormal neurotransmitter functioning. Mendel stated that human traits are determined by individual genes that function independently of other genes and environmental influences. Koch believed that many human diseases are caused by microbes that exert their effect independently of other microbes, environmental factors, and genes. The cause of most mental illnesses cannot be explained by neurotransmitters, genes, or infections alone. Instead, as stated by Yolken,⁸

Most common human diseases are caused by the interaction of environmental insults and susceptibility genes. Many of the susceptibility genes are diverse determinants of human response to environmental factors, including infections, and prevention or treatment of the infections may result in the effective treatment of complex disorders.

Neuropsychiatric disease is often associated with an interaction of environmental insults and susceptibility factors that frequently results in a pathological interaction including inflammation, oxidative stress, mitochondrial dysfunction, and excitotoxicity, which leads to neuronal dysfunction.³

Numerous studies document that infections, such as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, syphilis, hepatitis C, and zoonotic (animal) diseases, can cause mental illness.⁹⁻¹³ The same syndrome may be caused by different infections in different individuals, and the same infection can cause different syndromes in different individuals. For example, obsessive-compulsive disorder has been caused by infection with *Streptococcus*, *B burgdorferi*, Japanese B encephalitis virus, herpes simplex virus 1, Borna disease virus, Epstein-Barr virus, and *Mycoplasma*, as well as by the pandemic influenza of 1918¹⁴⁻¹⁶; I have also observed cases caused by Hong Kong influenza and coxsackie virus infection. Of course, many of these infections have also been shown to cause other psychiatric and somatic symptoms. Some infections result in residual injury even after the infection itself no longer persists, while other infections may persist in a chronic relapsing and remitting state. Chronic infections are most commonly viral, venereal, and vector-borne zoonotic.⁸

Tick-borne diseases and chronic infectious diseases

B burgdorferi, the principal organism associated with Lyme borreliosis, is one of the most complex bacteria known to man. In addition, a tick bite can presumably transmit more than 1 disease-causing organism. Thus, 2 major clinical hurdles in diagnosis and management are the absence of a clear therapeutic end point in treating Lyme borreliosis and the potential presence of tick-borne coinfections that may complicate the course of the illness.³ The more common interactive coinfections may be caused by *M fermentans*, *Mycoplasma pneumoniae*, *B microti*, *Babesia WA-1*, *Chlamydia pneumoniae*, *Ehrlichia*, *Anaplasma*, and *B henselae*, and multiple viruses and fungi.^{2,3,17} When multiple microbes grow together, they can promote immunosuppressive effects and cause marked symbiotic changes that alter their functioning.¹⁸

Neuroborreliosis is an infection within the brain; however, infections in the body that do not pass through the blood-brain barrier may also impact the brain indirectly via immune effects. All the clinical manifestations, acute or chronic, of infection with *B burgdorferi* are characterized by strong inflammation with the production of several proinflammatory and anti-inflammatory cytokines with an aberrant innate proinflammatory response¹⁹ and inflammatory brain changes.²⁰ Most of the dysfunction caused by these infections is associated with immune reactions.

Lyme borreliosis and other tick-borne infections are associated with a combination of inflammatory reactions and autoimmune symptoms. The proinflammatory cytokines associated with these infections increase indoleamine 2,3-dioxygenase, which decreases serotonin and kynurenic acid, a neuroprotective glutamate antagonist. In addition, the cytokines increase the level of quinolinic acid, an *N*-methyl d-aspartic acid (NMDA) agonist and neurotoxin, which contributes to the neurological and cognitive deficits seen in patients with tick-borne infections.²¹⁻²³ This change may produce over-stimulation of hippocampal (NMDA)

receptors leading to apoptosis and hippocampal atrophy. Hippocampal atrophy in the temporal lobes caused by NMDA over stimulation has been associated with depression and dementia.²⁴

Lyme borreliosis and other tick-borne infections can exist as an asymptomatic chronic carrier state, they can present with occasional or chronic fluctuating low-level symptoms, or they can lead to severe multisystem dysfunction and a multitude of psychiatric presentations.²

Assessment

Some helpful screening questions for a person with suspected late or complicated *B burgdorferi* infection are listed in **Table 2**. Positive responses require a thorough history, review of systems, and assessment of cognitive, emotional, vegetative, behavioral, psychiatric, neurological, and somatic symptoms.

TABLE 2

Screening for suspected late or complicated Lyme disease

1. Do you live or have you vacationed in areas that may expose you to ticks?
2. Have you engaged in activities that may have exposed you to ticks? expectations
3. Have family members, neighbors, or the family dog been infected?
4. Is there a history of a tick bite, possibly with a flu-like illness and/or a bull's-eye or other rash?
5. Is there a point at which the patient's health declined, followed by a relapsing progression and development of multisystemic symptoms, including cognitive, psychiatric, neurological, and physical symptoms?
6. Have antibiotics ever caused a sudden worsening followed by an improvement of symptoms?*

*Refer to Jarisch-Herxheimer reaction in Discussion section.

Lyme borreliosis and other tick-borne infections are clinical diagnoses. Although no test can rule out the possibility of infection,^{2,25,26} common laboratory testing may include Lyme IgG Western blot from a reliable laboratory, brain SPECT, and cognitive testing. Other diagnostic assessment may include polymerase chain reaction, C-6 enzyme-linked immunosorbent assays in spinal fluid, flow cytometry, and testing for coinfections. CD57 natural killer cell panel testing is useful for tracking clinical progress.²⁷

Caution should be taken because some patients may have an exacerbation of symptoms caused by a Jarisch-Herxheimer reaction (a short-term immunological reaction to antibiotic treatment that may include fevers, chills, head-aches, and myalgias) and may become acutely suicidal, violent, psychotic, and/or confused in response to antibiotic treatment.⁹ A trial course of antibiotics that causes a worsening of psychiatric symptoms followed by improvement suggests a Jarisch-Herxheimer reaction and can help support the impression that a chronic infectious process is contributing to psychiatric symptoms.

The differential diagnosis may include any medical or psychiatric condition, but particularly other conditions with complex presentations and fatigue, such as MS, lupus, and posttraumatic stress disorder.

Although co-occurring symptoms may be caused by multiple diseases, more commonly a single disease process can have multiple manifestations. The greater the comorbidity, the greater the likelihood that it is a systemic disease process with multiple manifestations. Multiple psychiatric syndromes, especially those with neurological and cognitive symptoms,

suggest a CNS pathological process, while significant psychiatric and somatic comorbidity suggest systemic disease. Significant comorbidity increases the suspicion of Lyme borreliosis and other tick-borne infections.

Comorbidity

Psychiatric and somatic comorbidity is the norm and Lyme borreliosis can often be associated with atypical presentations of psychiatric syndromes with relapsing and remitting progressive deterioration.^{12,13} For example, there may be an atypical presentation of attention-deficit/hyperactivity disorder (ADHD) with a predominance of executive dysfunction and sensory hyperacusis, panic disorder with attacks that last longer than 30 minutes, or presenile dementia.²⁸ In addition, borreliosis can exacerbate preexisting psychiatric illness. It has been my clinical observation that this is particularly apparent with preexisting ADHD, depression, and psychotic disorders. Chronically mentally ill homeless persons frequently sleep in parks, increasing their risk for Lyme borreliosis and other tick-borne infections, which could exacerbate illness severity.

Treatment

Although there is no FDA-approved treatment for the psychiatric symptoms associated with Lyme borreliosis, it has been my experience, as well as that of my colleagues, that many of the common psychopharmacological strategies for symptom reduction are beneficial. Patients with neuropsychiatric manifestations of Lyme borreliosis and other tick-borne infections often respond favorably to treatments that combine psychotropics and antimicrobials.^{2,29,30} Patients with inadequately treated late-stage infection may experience significant impairment and disability. Based on the collective experience of colleagues, the leading cause of death in borreliosis and tick-borne infections is believed to be suicide.³¹ Inadequately treated borreliosis and other tick-borne infections have been associated with autism spectrum disorder.^{11,32}

A mild case may improve following treatment with either psychotropics or antibiotics. Patients who have mostly been treated with antibiotics often need psychotropics, while patients who have mostly been treated with psychotropics often need antibiotics. The physician should prioritize which symptoms are most severe and contribute most toward perpetuating chronic illness and treat those first. If psychotropics are needed, the choice of drug type depends on the presenting symptoms.

Commonly, the most disabling neuropsychiatric symptoms include sleep disorders, fatigue, cognitive impairments, depression, anxiety, pain, and headaches. Because impaired sleep and chronic stress cause compromised immune functioning and contribute to fatigue and cognitive impairment, normalizing the circadian rhythm is often a treatment priority. Delta-sleep-promoting agents, such as pregabalin, trazodone, quetiapine, and tiagabine, are treatment options. Modafinil is often effective for excessive sleepiness, fatigue, cognitive impairment, and apathy.^{29,30,33}

Memantine can improve white matter dysfunction and processing speed, reduce word inventions (neologisms), improve word retrieval, and reduce "static and crackle in the head." In addition, better verbal comprehension, and better focus have been reported.³⁰ Atypicals can treat acute suicide risk. Mood stabilizers (anticonvulsants, atypicals, and lithium) can reduce aggression, migraines, and/or neuropathy and control seizures.^{29,30,34} Serotonin norepinephrine reuptake inhibitors can treat pain, anxiety, and depression. Doxepin in low doses is helpful for irritable gut. Acetylcholinesterase inhibitors are helpful for long-term memory impairments in late-stage disease. Although none of these are approved for treatment of neuropsychiatric symptoms associated with Lyme disease or other tick-borne infections, neither are they contraindicated, and there are no currently approved treatments. (We must treat with the best that we have, however flawed the evidence may be.) Prolonged antibiotic therapy may be useful and justifiable in patients with persistent symptoms of Lyme disease and coinfection with other tick-borne agents.^{2,10,35}

The controversy

Controversial issues surrounding Lyme disease include the reliability of laboratory tests, persistence of infections, clinical manifestations, pathophysiology, and treatment strategies. In 1975, a rheumatologist undertook an investigation using an acute infectious disease model

that focused primarily on the objective early, musculoskeletal (arthritis) symptoms and CNS symptoms; mental health capabilities were not considered. Some clinicians still believe that there is no later-stage encephalopathy and maintain the original, highly restrictive definition of Lyme disease from 1975. However, many reports have discussed the expanded complexity of the clinical presentations and pathophysiology, and the role of tick-borne and non-tick-borne interactive coinfections.³⁵⁻³⁸

Recognition of the mental impairments associated with these infections has been incorporated into a broader set of evidence-based guidelines from the National Guideline Clearinghouse for the treatment of Lyme disease.³⁹ Other evidence-based guidelines, endorsed by the Infectious Diseases Society of America (IDSA) and the American Academy of Neurology, are more restrictive and do not incorporate psychiatric morbidity associated with Lyme borreliosis and other tick-borne infections.^{40,41} Insurance companies were quick to adopt the more restrictive guidelines and the legal system responded by investigating the IDSA guidelines.⁴²

Since there are complex interactions between the brain, microbes, and the immune system, better communication is needed between psychiatrists, infectious disease specialists, and immunologists to reconcile the controversy.

Conclusion

Multisystemic diseases are often poorly managed because of the fragmentation in our health care system. In addition, patients with Lyme disease, similar to patients with psychiatric disorders, may have invisible disabilities and may have great difficulty with accessing adequate health care and disability coverage. Psychiatrists need to understand health care delivery issues and may be asked for opinions and assistance in these cases.

Additional information on neuro-psychiatric Lyme borreliosis is available from many online sources. Several of these are listed in **Table 3**.

TABLE 3

Web sites with information on neuropsychiatric Lyme disease

- Lyme Info: www.lymeinfo.net/neuropsych.html
- Lyme Disease Research Studies: www.columbia-lyme.org/index.html
- CDC Lyme Disease: www.cdc.gov/ncidod/diseases/submenus/sub_lyme.htm
- Mental Health and Illness. Neuropsychiatric Assessment Database: www.mentalhealthandillness.com/lymeframes.html
- National Guideline Clearinghouse: www.guideline.gov/search/searchresults.aspx?Type=3&txtSearch=lyme+disease&num=20
- Lyme Disease Association, Inc: www.lymediseaseassociation.org
- International Lyme and Associated Diseases Society (ILADS): www.ilads.org

Accessed October 17, 2007.

REFERENCE GUIDE

Therapeutic Agents Mentioned in This Article

Ceftriaxone (Rocephin)
Doxepin (Adapin, Sinequan)
Memantine (Namenda)
Modafinil (Provigil)

Pregabalin (Lyrica)
Quetiapine (Seroquel)
Tiagabine (Gabitril)
Trazodone (Desyrel)

Brand names are listed in parentheses only if a drug is not available generically and is marketed as no more than two trademarked or registered products. More familiar alternative generic designations may also be included parenthetically.

EVIDENCE-BASED MEDICINE:

- Cameron D, Gaito A, Harris N, et al; The International Lyme and Associated Disease Society. Evidence-based guidelines for the management of Lyme disease. Available at: www.ilads.org/files/ILADS_Guidelines.pdf. Accessed October 17, 2007.
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