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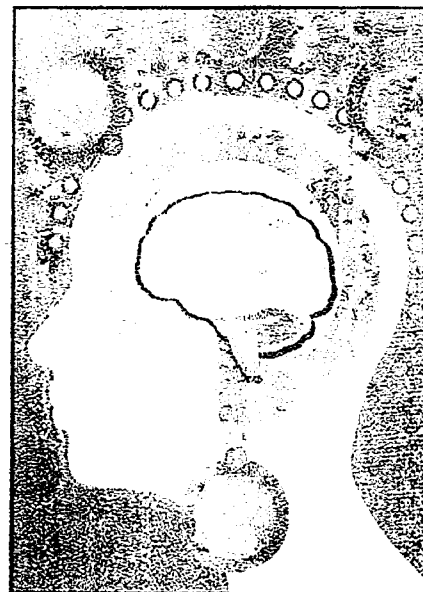
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Infections & Psychiatric Symptoms

Jose A. Yaryura-Tobias, MD

Guest Editor

Neuroscientific research supports links between certain infectious diseases and psychiatric presentations. This issue of *Psychiatric Annals* examines some of these relationships. Included are immunologic factors related to schizophrenia, the connection between rheumatic fever and obsessive-compulsive disorder, and psychological symptoms that patients with Lyme disease may exhibit.



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Lyme Borreliosis:

Neuropsychiatric Aspects and Neuropathology

Brian A. Fallon, MD; Benjamin J. Vaccaro; Megan Romano, BA; and Maria D. Clemente, MA

Lyme disease, the leading vector-borne disease in the United States, may present with psychiatric features. Consider the following cases.

Case 1. In early summer, a 34-year-old man, a previously healthy landscaper from Minnesota, developed a change in personality characterized by irritability, low frustration tolerance, spontaneous unprovoked tearfulness, and fatigue. The fatigue was quite severe, requiring up to 12 hours of sleep at night and daytime naps. Associated physical symptoms include diffuse myalgias and arthralgias, along with rare sharp shooting pains down his arms and intermittent migrating numbness in his extremities.

Case 2. In the fall, a 13-year-old girl from Maryland developed headaches that lasted all day and new-onset fears and neurobehavioral problems associated with distractibility, agitation at school, mild compulsive behaviors, intermittent

dyslexic errors, and hypersensitivity and intolerance to certain sounds. This girl, active in field hockey, recalled having seen a 2-inch red painless rash on her thigh about 4 months earlier that started small and expanded in size and was followed a few weeks later by unexplained severe low back and bilateral thigh pain that gradually remitted in intensity. Other symptoms included new-onset pain in the joints of her fingers.

Case 3. A 58-year-old man, an English teacher from northern California, developed memory problems such that he was unable to recall the names of his students or the class lesson he had taught the prior week. The memory loss was intermittent but worsening, associated with word retrieval errors. Completing the day at work seemed more difficult, as he had to fight back intense fatigue. On two occasions, he got lost in his own neighborhood; this lasted a few minutes

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and resolved. Two years earlier, he had had a flu-like illness followed by a very painful, tender right knee that could not be explained and resolved after 6 months, followed by his usual state of good health.

Each of the people in these cases was eventually diagnosed and treated for Lyme disease, but not before having been symptomatic for at least 1 year and having seen several doctors who had not thought to consider this diagnosis. These patients had been misdiagnosed as having either a primary psychiatric disorder or chronic fatigue syndrome. Although each of the patients eventually did quite well, the treatment involved repeated courses of antibiotics and adjunctive therapies. Had the patients' infection been detected earlier, the repeated courses of treatment may not have been necessary. Common features of each of these cases include a multisystemic illness causing fatigue, rheumatic, neurologic, and psychiatric symptoms.

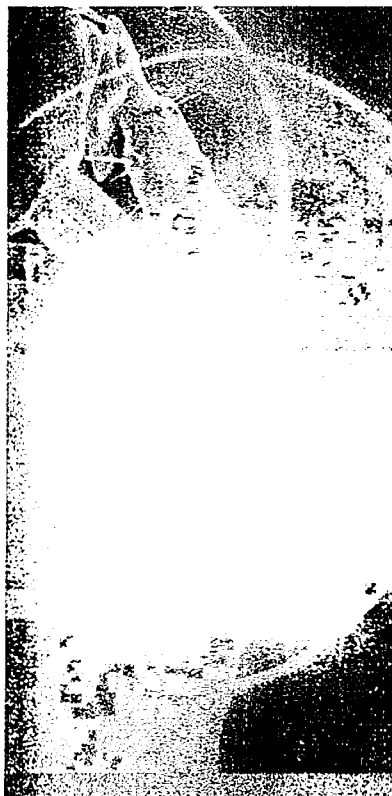
The goal of this article is to alert clinicians to the neurologic and psychiatric aspects of Lyme disease, to highlight the differential diagnosis, and to briefly address the neuropathology and different treatment strategies. Although it may seem outside of the realm of the mental health clinician's responsibilities to become knowledgeable in the neurologic and medical aspects of Lyme disease, mental health clinicians need to have an

in-depth knowledge of whatever may cause significant psychiatric symptoms in their patients. Failure to recognize and treat the underlying infectious disease can lead to severe neuropsychiatric disability and, in some cases, death due to suicide. Recognition and appropriate treatment, on the other hand, can be one of the most rewarding experiences in clinical practice.

HISTORY

Lyme disease, a multisystemic illness with numerous and diverse clinical manifestations, was first identified in the United States in 1975 as a migrating large joint arthritic illness that emerged after an erythema migrans skin lesion.¹ During the following 10 years, the psychiatric and central and peripheral neurologic features were described, and its relationship to older, similar neurologic illness in Europe (eg, Bannwarth's syndrome, Garin-Bujadoux syndrome) was recognized.² Because of its initial presentation as a skin rash, its subsequent protean multisystemic manifestations with potentially severe neuropsychiatric symptoms, and its spirochetal etiology (a spiral shaped bacterium, *Borrelia burgdorferi*), Lyme disease became known as the "new Great Imitator," replacing syphilis for that distinction.

Lyme disease has reached epidemic status in the US and currently is the most frequently diagnosed vector-borne illness. To standardize the epidemiologic monitoring of Lyme disease in the United States, the Centers for Disease Control and Prevention (CDC) created a case definition that focused on the skin, arthritic, and early neurologic manifestations.³ While helpful for surveillance, these criteria failed to include the later neuropsychiatric manifestations of the disease. Clinicians relying on these clinical criteria as the sole guideline for clinical diagnosis therefore would fail to recognize and diagnose late-stage neuropsychiatric symptoms of Lyme disease.



The presence of symptoms affecting the neurologic (central and peripheral) and rheumatologic systems should serve as a clear sign for a clinician to consider Lyme disease. Although some patients with neuropsychiatric Lyme disease do not have rheumatologic symptoms, most do.

DISTRIBUTION AND RISK

Cases of Lyme disease have been reported throughout the US, with the vast majority of cases emerging from three areas: the Northeast, the upper Midwest, and the Pacific coastal region. While clinicians in areas not heavily endemic for Lyme disease may imagine that it will not affect their patients, this is a mistake. Reports of Lyme disease have emerged from 49 of the 50 contiguous states. Further, patients may reside in one area but have contracted Lyme disease elsewhere, through either travel or prior residence.

B. burgdorferi is transmitted by ixodes ticks and therefore can be easily spread by the carriers of these ticks, which include mice, deer, and birds. The ticks prefer leafy wooded areas, so those at greatest risk for this disease are those who spend time outdoors (eg, children, hikers, golfers, landscapers) and those with pets that travel freely through low lying brush and leaf litter.

CLINICAL DIAGNOSIS

Despite advances in diagnostic testing, Lyme disease remains a diagnosis that is made based on the clinical presentation. The presence of symptoms affecting the neurologic (central and peripheral) and rheumatologic systems should serve as a clear sign for a clinician to consider Lyme disease. Although some patients with neuropsychiatric Lyme disease do not have rheumatologic symptoms, most do. Laboratory and neuroimaging tests are helpful to support the clinical impression, but the diagnosis can be made even in the absence of a positive test for Lyme disease. To assist the mental health and primary clinician in the clinical diagnosis of Lyme disease, the typical symptom profile is outlined below.

Early Lyme Disease

Approximately 24 hours after the bite of an infected tick, the borrelial spirochete is transmitted to the skin. The

erthema migrans rash that occurs shortly thereafter is pathognomonic for Lyme disease; mostly commonly a red circular rash that expands over time, the rash may have more diverse features as well and may be mistaken as a spider bite. Treatment with oral antibiotics at this stage often is curative.

Disseminated Lyme Disease

Once the spirochete invades the vascular system, it is spread hematogenously to organs that may include the heart (causing conduction block or pericarditis), the liver (causing mild hepatitis), the joints (causing pain, tenderness, or inflammation), the eyes (causing conjunctivitis), and the nervous system. The initial nervous system manifestation of headache may be accompanied by the typical general systemic symptoms of "a bad flu," with myalgia, arthralgia, prolonged fatigue, and low-grade fever. Because more than one-third of patients may not recall a tick bite or rash, the initial presentation of Lyme disease may be neuropsychiatric.

Early Disseminated Neurologic Lyme Disease

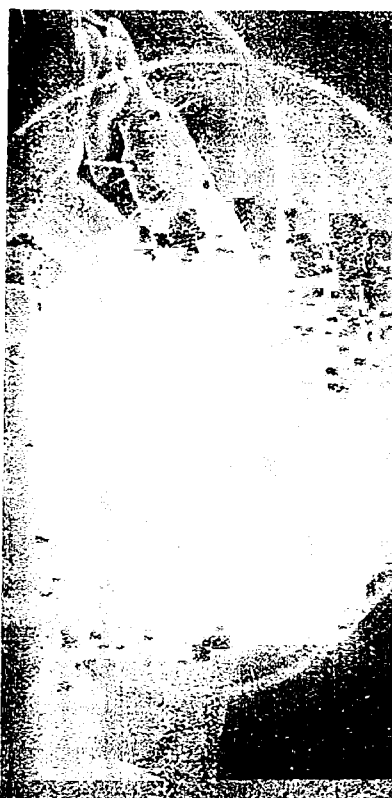
This is characterized by headaches, stiff neck, photophobia, and nausea.

Meningitis

Typically, headaches related to meningitis fluctuate in intensity from severe to mild. There may be associated nausea, vomiting, photophobia, or pain on eye motion. At this stage, a lymphocytic pleocytosis may be seen with mildly elevated protein.

Encephalitis

Common symptoms of cerebral involvement include somnolence, emotional lability with tearfulness and irritability, cognitive problems (poor memory, slower processing speed, impaired concentration), balance problems, sensory hyperarousal, and behavioral changes.



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Less commonly associated symptoms include choreiform movements or seizures. An electroencephalogram may show a mild slowing.

Cranial Neuritis

Facial nerve palsy is the most common manifestation of cranial neuritis related to Lyme disease. If cranial nerve VII palsy is bilateral, then the odds of Lyme disease being the etiology are increased significantly. The cranial nerve (CN) palsy usually begins within days to weeks of the initial infection. If the trigeminal nerve (CN V) is involved, abnormalities in sensation (eg, spontaneous facial pain) or deficits in light touch, pinprick, and temperature may occur. Impaired peripheral optic nerve may result in the patient complaining of central vision appearing cloudy. If CN III, IV, or VI are affected, the patient may present with double vision and on exam manifest ptosis, anisocoria, or mydriasis. If CN VIII is involved, there may be tinnitus, loss of hearing, vertigo, or ataxia.

Radiculoneuritis

Local pain, most commonly affecting the shoulder, may be accompanied by radicular pain and motor weakness. The sensory symptom may consist of loss or of increased sensitivity to touch or temperature, sharp or burning pain radiating along a dermatome, or numbness/pins and needles.

CHRONIC OR LATE NEUROLOGIC LYME DISEASE

In this stage, the patient may present with symptoms of neuropathies, encephalopathy, or encephalomyelitis.

Neuropathies

Radiculoneuropathy related to Lyme disease most often is characterized by symmetric or asymmetric sensory symptoms, such as distal paresthesias or radicular pain in the limbs. The paresthesias usually manifest in a "stocking-

glove" distribution and are experienced as numbness, tingling, and "pins and needles." On exam, sensory loss in all modalities may be noted.

The radicular pain may be similar to that seen in early neurologic Lyme and is characterized by pain in a dermatomal distribution, most often centered in the spine and radiating into the limbs or trunks. Electrophysiologic studies may show a mild sensorimotor axon loss, a reduction in distal action potential amplitudes, or denervation of distal and proximal (paraspinal) muscles. Differential diagnosis of the radiculoneuropathy requires exclusion of common alternative causes of distal paresthesias, such as diabetic and toxic-metabolic neuropathies, and of radicular pain, such as structural compression.

Encephalopathy

Late-stage encephalopathy related to Lyme disease ranges from mild to severe but most often is mild and primarily affects speed of mental processing, verbal fluency and retrieval, and short-term memory. Patients may report getting lost in familiar places, trouble with multitasking, trouble finding words, and inability to recall conversations or details of events. Oftentimes, these patients describe their mental state as a "brain fog." Neuropsychological testing is essential to identify the affected areas and to objectify the extent of impairment both for current treatment planning and for future determination of the effect of treatment.

Encephalomyelitis

More common in Europe than in the United States, Lyme encephalomyelitis may result in encephalitis, chorea, cerebellar ataxia, and seizures. In some cases, it may be misdiagnosed as multiple sclerosis.

Psychiatric Disturbances

Psychiatric symptoms commonly seen in later stage Lyme disease include

sleep disturbance, irritability, and sensory hyperarousal. The sleep disturbance may manifest as restless sleep with frequent awakening or as extraordinarily long and deep sleep. Some patients may develop a frank sleep disorder, such as central apnea or narcolepsy. One of our patients, a teenage girl, developed Klein-Levin syndrome, characterized by 5-day periods every 6 weeks of severe hypersomnolence, hyperphagia, hypersexuality, and personality change when awake, followed by no pathology between episodes and amnesia for her behaviors during the hypersomnolent period.

The sensory hyperarousal may affect hearing, leading to a learned avoidance of situations (such as restaurants, movie theaters), or affect vision, leading to the wearing of sunglasses or requiring diminution of lighting indoors. The experience of sensory hyperarousal can be similar to a kindling phenomenon in which small amounts of stimulation are tolerated, but as these increase in number or intensity, a sensory tolerance threshold is exceeded, which then results in decreased tolerance for previously tolerated stimuli. When the threshold of tolerance is exceeded, patients may act as if assaulted, fearing both the stimulus and the source of the stimulus, at times attributing malevolent intent and thereby becoming paranoid.

The international literature on Lyme disease has reported a wide range of psychiatric manifestations of Lyme disease, ranging from the common ones of mood lability, depression, and anxiety to the less common ones of psychosis, mania, obsessive-compulsive disorders, and an anorexia-like syndrome.⁴

Chronic Fatigue

The fatigue and somnolence that characterize Lyme disease in both the early and later stages can be quite profound with a need for increased nighttime duration and naps during the day. The differential diagnosis for fatigue is extensive,

but the differential should certainly exclude sleep apnea and major depression.

DIFFERENTIAL DIAGNOSIS

The chief concern when diagnosing Lyme disease is to exclude other diagnoses that may manifest with relapsing and remitting symptoms that are diffuse and multifocal affecting the central and peripheral nervous system symptoms. The most common conditions to consider would include serum sickness, systemic lupus erythematosus, hepatitis B and C, infectious mononucleosis, syphilis, other viral and rickettsial infections, mycoplasma pneumoniae, leptospirosis, sarcoidosis, polyarteritis nodosa, Behçet's syndrome, and multiple sclerosis.

DIAGNOSTIC TESTS

While recalling that the diagnosis of Lyme disease can be made by clinical presentation alone, there are certain tests that are used to assist in the diagnosis. The two most currently employed serologic tests for Lyme are the enzyme-linked immunosorbent assay (ELISA) and the Western blot (immunoblot). Although the CDC recommends using the ELISA for screening, in patients with late-stage or chronic Lyme disease, the ELISA has a sensitivity rate of only 55% to 80% among patients with a history of well-defined and documented Lyme disease. Therefore, as a screening test, the ELISA is inadequate. The CDC is currently investigating the usefulness of a new more specific test for Lyme disease, the C6 Peptide ELISA.⁵ This is available at commercial laboratories. If a patient tests positive on the C6 ELISA, then that is good evidence that the patient's immune system has generated specific antibodies against *B. burgdorferi*.

Many clinicians and researchers rely primarily on the Western blot, as this test provides more information in helping to guide the clinician diagnostically. The current CDC criteria for a positive IgG Western blot include a minimum of

5 of the following 10 bands: 93 kDa, 66 kDa, 58 kDa, 45 kDa, 41 kDa, 39 kDa, 30 kDa, 28 kDa, 23 kDa, and 18 kDa. A positive IgM must include two of the following bands: 23 kDa, 39 kDa, and 41 kDa. These bands, labeled as "Lyme-specific," were chosen because these were the most frequently seen bands among patients with the classic clinical profile of Lyme disease.

Not included in the above criteria are two of the most specific bands, the 31 kDa and 34 kDa, representing the OspA and OspB antigens. Although these are remarkably specific to the *B. burgdoferi* spirochete, they were not included in the CDC's list because they were not found in the top 10 most frequent bands. The problem is that other bands that are less specific for Lyme disease were included, such as the 41 kDa band, which many noninfected healthy controls also carry. Unless a laboratory is asked by the clinician to "report all bands," the standard report will only report the presence or absence of the top 10 IgG bands, thus depriving the clinician of valuable laboratory data.

Another problem with the Western blot is that different laboratories use different techniques and the subjective reading and interpretation of whether a blot's banding pattern is of sufficient density to be considered positive requires considerable expertise. Some labs report the intensity of each banding pattern (eg, IGeneX), whereas most others report only a positive or negative result.

Polymerase chain reactions (PCR) tests are among the most specific diagnostic tests for Lyme disease in that the test detects the genetic material of the spirochete. However, because *B. burgdoferi* is a predominately tissue tropic bacterium, its DNA can only rarely be detected in the blood, CSF, or urine.

In patients with neuropsychiatric symptoms, all efforts should be made before starting treatment to confirm the clinical diagnosis. The best demonstra-



Few patients with neuropsychiatric Lyme disease will have either a positive PCR or elevated intrathecal Ab production. Nevertheless, when either of these is demonstrated, both the patient and physician can be confident in the diagnosis of neurologic Lyme disease.

tion of central nervous system invasion by *Borrelia* is provided by either a positive PCR assay detecting DNA in the CSF or a positive intrathecal Ab index for Bb antibody. The intrathecal index represents a ratio of the amount of Bb specific Ab in the CSF over the amount in the serum; an elevation greater than 1.0 suggests that there is preferential production of antibodies in the CSF and supports the assumption of sequestration of spirochete.

Few patients with neuropsychiatric Lyme disease will have either a positive PCR or elevated intrathecal Ab production. Nevertheless, when either of these is demonstrated, both the patient and physician can be confident in the diagnosis of neurologic Lyme disease. This is of tremendous value both to the clinician who seeks to ameliorate the patient's symptoms and to the patient who seeks insurance reimbursement for antibiotic treatment that can be quite costly.

When the serum and CSF are sent for intrathecal testing (and these should be drawn close in time), the clinician should also ask for Western blot testing on each of the fluids. A comparison can then be made of the bands identified in the CSF versus the serum, and if unique bands are identified in the CSF that would be another indicator of intrathecal production. Other CSF tests that should be conducted include protein, glucose, cell count, and oligoclonal bands. Patients with neurologic Lyme disease rarely have more than one oligoclonal band. Low elevations of protein level may be seen, although this is nonspecific. White blood cell count may be elevated, particularly in early neurologic Lyme disease.

IMAGING STUDIES

Structural Brain Imaging

Approximately 40% of patients with neurologic Lyme disease have been reported to have small white matter hyperintense areas on T2 and FLAIR magnetic resonance imaging sequences. These hyperintense areas may represent inflamma-

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tion or areas of demyelination. The clinician should be aware that white matter hyperintensities increase in prevalence as patients age and may be induced by other factors, such as smoking or ischemia. When periventricular in distribution, confluent, and enhancing on gadolinium scans, these white matter hyperintensities can appear very similar to the hyperintensities observed among patients with multiple sclerosis. Gadolinium enhancement, however, would be unusual among patients with Lyme disease.

Functional Brain Imaging

Functional brain imaging with single photon emission computed tomography (SPECT) has become an important part of the evaluation of the patient with suspected neuropsychiatric Lyme disease. Research during the past decade demonstrates that patients with Lyme disease typically have a brain SPECT scan demonstrating a pattern of decreased blood flow that is decreased diffusely, but in a heterogeneous manner.^{6,7} White matter hypoperfusion is also often seen.⁸ This pattern of hypoperfusion is partially reversible after antibiotic therapy. This pattern is not diagnostic of Lyme disease and can be seen in other diseases such as vasculitides, chronic cocaine use, or other encephalitides.

How, then, can a brain SPECT be helpful? If a patient with psychiatric symptoms presents with either a poor response to standard treatment or atypical features, then an underlying medical cause should be investigated more thoroughly. If the history of the patient includes exposure to a tick-infested area and a multisystemic illness including many of the typical Lyme symptoms noted above, and if other possible causes of heterogeneous hypoperfusion are ruled out, then a SPECT scan with this typical pattern may suggest that the cause of the psychiatric symptoms may be more likely due to Lyme disease than to a primary psychiatric disorder.⁹ Research is

now ongoing to determine the sensitivity and specificity of the clinical use of SPECT imaging for the differential diagnosis of Lyme disease.

It is important to highlight that SPECT imaging is not particularly useful among patients 20 or younger, as brain perfusion typically appears normal even in the presence of neurologic Lyme disease. However, if the brain SPECT scan does show a pattern of heterogeneous hypoperfusion in an adolescent, for example, that would suggest a greater degree of brain involvement than a comparable scan from an adult.

NEUROPATHOLOGY AND MECHANISMS OF IMMUNE EVASION AND PERSISTENCE

Neurologic injury in Bb infection may result from direct action of the bacteria or bacterial products or from indirect effects of an activated immune system, as in cross-reactive antibodies or the cellular immune response.¹⁰ Evidence for direct action include the fact that *B. burgdoferi* binds to host tissue and has surface lipoproteins which have proinflammatory properties; an immune response amplified by acute or persistent infection can cause damage or dysfunction. Neurologic involvement in chronic Lyme disease has been shown to be associated with elevated levels of pro-inflammatory cytokines, such as interleukin 6 and tumor necrosis factor alpha.¹¹

B. burgdoferi are atypical gram-negative bacteria that may survive in the human host for years¹² and persist despite treatment.^{13,14} This survival results from an interplay between spirochete virulence and the human host response. For example, Bb preferentially displays surface lipoproteins with distinct functions depending upon the environment in which it resides (eg, the tick versus the human, the skin versus the central nervous system). In the mammalian host, this environment includes areas of different temperature, areas of dif-

ferent pH, and the humoral and cellular immune response — all of which can influence spirochetal gene expression and recombination. It has been demonstrated, for example, that Bb uses the host proinflammatory cytokine response (IL12 and interferon gamma) to promote genetic recombination during infection; this has been shown to facilitate the ability of the spirochete to persist in vivo, presumably by helping the spirochetes to avoid recognition and destruction by Bb specific antibody responses.¹⁵

Peripheral nerve dysfunction in Lyme disease is associated with mononuclear perivascular infiltrations without necrotizing vasculitis. CNS dysfunction may result when *B. burgdoferi* spirochetes increase the permeability of the blood-brain barrier and thereby cross and bind to astrocytes (the nearest neighbor to the brain capillaries) and oligodendrocytes. Changes in the permeability of the blood-brain barrier have been observed as soon as 12 hours after infection in animal models. The argument for long-term persistence in the CNS is supported by the affinity and adherence of Bb to neural and glial cells and may explain why it is only seldom isolated from the CSF. Glial cells, such as astrocytes, may respond to Bb and cause CNS dysfunction by producing pro-inflammatory cytokines. Nitric oxide production, for example, may result from the microglial inflammatory response to Bb invasion and result in neuronal and oligodendroglial injury.

Evidence addressing the difficulty in eradicating *Borrelia* bacteria from the CNS was released by Pachner et al.¹⁶ in a study conducted on nonhuman primates and spirochetal density in various tissues. The data indicated that spirochetal density of the CNS was equivalent in both immunosuppressed and immunocompetent nonhuman primates infected for the same 3-month duration. This observation did not hold true for other tissues, however, including peripheral nervous, cardiac, and muscle tissue. This led the

authors to postulate that spirochetes in the CNS may be isolated from the host's systemic immune system.

Additional findings from other researchers suggest another possible mechanism for immune evasion. *B. burgdorferi* spirochetes are capable of entering cells, such as fibroblasts, B lymphocytes, and endothelial cells. Inside cells, the *Borrelia* will not be detected by immune surveillance. Of equal importance is that many commonly used antibiotics, such as the penicillins and other β lactams, are not effective against intracellular bacteria.

TREATMENT

The treatment of Lyme disease, when detected early, consists of 3 weeks of oral antibiotics, most typically amoxicillin or doxycycline. In neurologic Lyme disease, the recommendation is for 4 weeks of intravenously administered ceftriaxone or cefotaxime because of the bacteria's ability to penetrate the blood-brain barrier. Approximately 60% of patients with neurologic Lyme disease respond well to intravenous ceftriaxone; 20% respond but relapse, and 20% do not respond.¹⁷ The optimal treatment for patients with relapsing or persistent symptoms is unknown, with one controlled study indicating that repeated therapy is not helpful¹⁸ and two other placebo-controlled studies indicating that repeated intravenous therapy is helpful for patients with persistent Lyme fatigue¹⁹ and persistent Lyme encephalopathy.²⁰ There exists no standard treatment that guarantees complete symptom resolution.

Symptoms may persist after treatment for multiple reasons. These include low-grade persistent infection; sequestration of the spirochete in areas where antibiotic penetration may be inadequate (eg, CNS, intracellular); unresolved damage or dysfunction from past spirochetal

presence; an activated autoimmune response; incorrect diagnosis; or presence of an undetected and untreated tick-borne co-infection which may suppress the immune response or present with Lyme-like features (as in Babesiosis).

SUMMARY

Lyme disease can be a complex, multisystemic disease that causes psychiatric and neurologic symptoms. The spirochete *B. burgdorferi* is capable of remarkable antigenic variation, immune evasion, and persistence in the human host. Optimal duration of treatment for patients with chronic Lyme disease remains uncertain. The mental health practitioner can be of help primarily in identifying patients with undetected Lyme disease, guiding them to appropriate laboratory tests and diagnosticians, and providing support through the uncertainties regarding course and treatment.

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