Dispelling the Chronic Lyme Disease Myth

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Abstract

Lyme disease is a tick-borne illness endemic to Minnesota that can have potentially severe complications. As the incidence of lyme disease continues to increase, it is important for physicians in Minnesota to become familiar with its clinical aspects, including the concept of "chronic Lyme disease." Chronic Lyme disease is a misnomer that is often applied to patients with nonspecific presentations who may or may not have a history of infection with *Borrelia burgdorferi*, the agent that causes lyme disease. When a patient does present with persistent nonspecific symptoms attributed to chronic Lyme disease, clinicians should ascertain the presence of objective manifestations, obtain laboratory results, and get a history of tick exposure. If active infection with *B. burgdorferi* is unlikely, they should avoid prescribing empiric antibiotic therapy and instead thoroughly evaluate the patient for other possible causes of the complaints and recommend appropriate care.

Lyme disease is a tick-borne illness caused by the extracellular bacterium *Borrelia burgdorferi*. In recent years, the expansion of the vector tick (the blacklegged tick or deer tick, *Ixodes scapularis*) into new areas of Minnesota and the increasing incidence of Lyme disease in the state have heightened public health [1,2]. Therefore, it is essential for clinicians to become familiar with the symptoms of Lyme disease and to know how to treat it, especially if they care

for patients who reside in or visit forested areas in east central, north central, and southeastern Minnesota and western Wisconsin, where blacklegged ticks are common.

Although increased awareness of Lyme disease is important, overdiagnosis and overtreatment of the disease can happen. “Chronic Lyme disease" is a loosely defined term that is sometimes applied to patients who present with a constellation of nonspecific or subjective complaints. These patients often request or are treated with repeated or prolonged antibiotic therapy.

This article examines the clinical evidence for the condition inaccurately referred to as chronic Lyme disease and explains why evidence-based treatment guidelines advise against the use of long-term antibiotic therapy for patients believing they have this diagnosis. Directing patients toward proper treatment options is also discussed.

Diagnosing and Treating Lyme Disease

Early localized Lyme disease arises within 3 to 30 days after being bitten by an infected blacklegged tick. It typically, but not always, manifests as a characteristic erythema migrans (EM) rash at the site of the bite. Regional lymphadenopathy with or without fever may be seen as well. Unrecognized or untreated infection may develop into early disseminated Lyme disease, then turn into late Lyme disease weeks or months later. Both early disseminated and late Lyme disease can be characterized by multiple EM lesions, constitutional signs and symptoms, generalized lymphadenopathy, intermittent or chronic oligoarticular arthritis of the large joints (involving objective swelling), peripheral or central nervous system involvement (radiculoneuropathy; cranial neuritis, mononeuropathy, lymphocytic meningitis, and, in rare cases, encephalopathy or encephalomyelitis), or cardiac involvement (atrioventricular heart block or myopericarditls). [3] Repeat exposure to blacklegged tick bites can lead to reinfection with *B. burgdorferi* and recurrence of Lyme disease. [4]

When an EM rash is present, early localized or disseminated Lyme disease can be diagnosed on the basis of the distinct lesion alone. During the acute phase of infection, the EM lesion frequently manifests before the development of detectable antibody to *B. burgdorferi*. Thus the sensitivity of serological testing during this phase may be diminished. [3,5] When the patient has no EM lesion, laboratory confirmation of *B. burgdorferi* infection must be present to implicate Lyme disease.

The Centers for Disease Control and Prevention (CDC) recommends a 2-tiered serologic testing protocol, in which serum specimens that are positive or equivocal by enzyme immunoassay (EIA) or immunofluorescent assay (IFA) screening are followed with Western immunoblot testing using well-established interpretive criteria. [3,6] These criteria specify that an immunoglobulin M (IgM) immunoblot is considered positive if 2 of 3 tested bands (24 kDa, 39 kDa, or 41 kDa) are present and that an immunoglobulin G (IgG) immunoblot is considered positive if 5 of 10 tested bands (18 kDa, 21 kDa, 28 kDa, 30 kDa, 39 kDa, 41 kDa, 45 kDa, 58 kDa, 66 kDa, or 93 kDa) are present. Testing for both lgM and lgG antibody should be performed if immunoblot is used during the first 4 weeks of illness. However, testing is not recommended for early localized Lyme

disease with a single EM lesion. At 4 weeks after illness onset, the CDC recommends relying on IgG results, as IgM findings at this stage of infection that are not accompanied by positive IgG findings likely represent false-positive results. [6] In addition to the 2-tiered serological assay, some manifestations of early disseminated or late Lyme disease may also warrant testing of a convalescent-phase serum sample (for instance, when the initial Western immunoblot analysis is equivocal), testing for intrathecal antibodies in cerebrospinal fluid, or polymerase chain reaction (PCR) testing of cerebrospinal or joint fluid. [3,5]

A clinical diagnosis of Lyme disease should also involve consideration of exposure to blacklegged ticks, either through a recognized bite or time spent in wooded, tick-endemic habitats. Positive laboratory findings should be interpreted in the context of whether the patient has lived or spent time in an area endemic to Lyme disease prior to symptom onset, as a test's positive predictive value diminishes proportionately with underlying disease prevalence. [7]

Appropriate antibiotic treatment that adheres to guidelines published by the Infectious Diseases Society of America (IDSA) is highly effective for resolving *B. burgdorferi* infection. [3,8-11] Because of the inverse relationship between the stage of Lyme disease and the time it takes for the illness to resolve after antibiotic therapy is initiated, late Lyme disease signs often wane slowly; joint effusions, for instance, may take 1 to 3 months to resolve. [12] Antibiotic therapies for various stages of lyme disease include the preferred oral agents (doxycycline, amoxicillin, or cefuroxime axetil) for 10 to 28 days or parenteral agents (ceftriaxone, cefotaxime, or penicillin G) for 2 to 4 weeks. Retreatment with intravenous ceftriaxone is needed in rare cases in which patients with Lyme arthritis fail to respond to a month of oral doxycycline; generally, it is not advised for other manifestations. [3] Claims that *B. burgdorferi* spirochetes can persist after appropriate antibiotic treatment appear to have been based on unreliable laboratory methodology. [13-18]

Following treatment for EM-documented or laboratory confirmed Lyme disease, some patients may continue to experience or subsequently develop nonspecific symptoms such as fatigue, musculoskeletal pain, and neurocognitive problems. These symptoms are not caused by an active *B. burgdorferi* infection and generally resolve within a few months. A smaller proportion of patients (0.5% to 13.1% of those with EM) experience symptoms for months, even years, following treatment. [19] This is known as post Lyme disease syndrome. The syndrome is most likely explained by a postinfectious inflammatory process, unrecognized and/or untreated coinfection with another tick-borne pathogen, or an idiopathic process unrelated to the previous Lyme disease diagnosis. [3,17,18] Similar nonspecific symptoms are also present in up to 30% of the population. [17,18]

Chronic Lyme Disease

Some patients, advocates, and practitioners apply the term chronic Lyme disease to a broad set of persistent and nonspecific complaints including fatigue, myalgias, arthralgias, headache, and memory loss. The topic was recently reviewed by Feder et al., who proposed that chronic Lyme

disease comprises multiple diagnostic categories, one of which is post-Lyme disease syndrome. [18]. Other patients who believe they have chronic Lyme disease may be seeking an alternative explanation to an already-diagnosed chronic illness such as multiple sclerosis or ankylosing spondylitis.

According to Feder et al., the chronic Lyme disease diagnosis also has been applied to patients with nonspecific complaints who lack any objective clinical findings of Lyme disease and have negative serologic studies for the condition. [18] Without laboratory evidence of *B. burgdorferi* infection these patients' complaints are unlikely to be caused by Lyme disease. In addition, patients with chronic subjective symptoms who have antibody to *B. burgdorferi* may claim to have chronic lyme disease. Without objective clinical findings, however, the positive predictive value of Lyme disease serology is low. [18] These patients may have a positive lgM immunoblot or a few (<5/10) positive bands on lgG immunoblot, neither of which is compatible with late manifestations of Lyme disease.

For these reasons, the term chronic Lyme disease is a misnomer. [18] Well-intentioned physicians often reinforce a patient's fixation on the diagnosis by empirically prescribing antibiotics for those with nonspecific symptoms and negative or nondiagnostic Lyme serology or those with nonspecific symptoms and positive Lyme disease serology. Providers sometimes send blood samples to "Lyme specialty" laboratories that perform serologic tests interpreted by criteria that are not evidence-based. When the symptoms persist in spite of oral antibiotics, the patient often seeks additional information on the Internet or from alternative sources, much of which is inaccurate. [20] This often leads to further courses of antibiotic treatment without demonstrable clinical benefit, a problem that underscores the need for careful clinical evaluation during the initial patient visit.

Antibiotic Therapy and Chronic Lyme Disease

Complaints of chronic Lyme disease rarely warrant new or continued antimicrobial therapy directed against *B. burgdorferi*. However, patients who are diagnosed with chronic Lyme disease frequently undergo long-term courses of oral or parenteral antibiotics. The medical research community, including the IDSA, has thoroughly examined and refuted the case for long-term antibiotic treatment of patients with persistent symptoms attributed to Lyme disease. [3,21] Four recent trials have failed to demonstrate any lasting benefits of prolonged antibiotic therapy for patients with post-lyme disease syndrome. [8,9,22,23] Because persistent symptoms in this population are not the result of active infection with *B. burgdorferi*, nonantimicrobial effects, such.as the placebo effect or the anti-inflammatory activity of some antibiotics (eg, tetracycline and its derivatives), may explain transitory improvements during antibiotic therapy. [18]

In the absence of direct antimicrobial benefit, the risk of serious adverse effects outweighs any benefits qf long-term antibiotic administration. In 1999, a 30-year-old Iowa woman died from septic embolic complications of an infected central venous catheter used for long-term IV

antibiotic treatment of purported chronic Lyme disease. [24] In a recent trial examining the efficacy of a 12-week course of either IV ceftriaxone or placebo for patients with post-Lyme disease syndrome, 6 of 23 (26%) patients given IV ceftriaxone experienced adverse events, including venous thrombosis, allergic reactions, or cholecystitis; in addition, 1 of 14 (7%) patients on IV placebo developed a systemic staphylococcal infection. [22] Reports of other major adverse events associated with Lyme disease treatment have included antibiotic-associated *Clostridium difficile* infection, septic thrombophlebitis, neutropenia, serum sickness, jaundice, IV catheter-associated bloodstream infection, anaphylaxis, pulmonary embolism, and gastrointestinal bleeding. [8,23,25]

Patients who believe they have chronic Lyme disease frequently undergo other unproven and potentially dangerous treatments. The IDSA guidelines recommend against the following therapies for lyme disease: combined antimicrobial therapies, pulsed-dosing, unproven antibiotics such as telithromycin or metronidazole, anti-babesiosis or anti-Bartonella treatment, hyperbaric oxygen therapy, fever therapy, IV immunoglobulin, ozone, cholestyramine, IV hydrogen peroxide, nutritional supplements, or injections of magnesium or bismuth. [3]

Addressing Patients' Needs

Primary care physicians and specialists alike may encounter a number of diagnostic and treatment challenges when patients present with nonspecific symptoms they believe are caused by Lyme disease. Clinicians seeing patients with nonspecific symptoms should evaluate them for a history of blacklegged tick exposure before symptom onset, document objective manifestations of Lyme disease, and confirm the clinical suspicion of active infection with *B. burgdorferi* using validated serologic testing methods. Interpretation of serologic findings must be made in the context of the presenting stage of illness. Without a more likely alternative diagnosis, Lyme disease diagnosed by this method should be treated according to established guidelines unless the patient has already undergone appropriate treatment. [3] For patients with post-Lyme disease syndrome, a clinician should verify that the previous treatment was appropriate and in accordance with current recommendations. In the absence of positive serologic evidence or objective clinical findings, clinicians should avoid making a tentative diagnosis of Lyme disease, as empirical treatment may cement the diagnosis in the patient's mind and hamper further diagnostic efforts. Instead, they should explore other explanations for the patient's complaints such as fibromyalgia, depression, or inflammatory rheumatologic disorder.

Dissuading patients who are convinced that they have chronic Lyme disease may be difficult. It often means disagreeing with another physician, the content of a website valued by the patient, or the opinions of a Lyme disease support group. To redirect a patient away from this diagnosis, the clinician should engage the patient in a straightforward yet empathetic conversation about Lyme disease diagnosis, treatment, and prognosis. With post-Lyme disease patients, the clinician must explain that it may take weeks or months for their headaches, achiness, fatigue, and other subjective symptoms to resolve and that this delay does not mean that treatment has

failed. Clinicians should also explain the hazards associated with unnecessary antibiotic therapy, especially when administered intravenously. As patients increasingly turn to the Internet for information, they should be encouraged to seek out websites that provide evidence-based information about diagnosis and treatment of Lyme disease such as those provided by the CDC, the Minnesota Department of Health, or Mayo Clinic and be cautioned about the multitude of sites that advocate unproven therapies. [20] It is important to make it clear that rejection of a chronic Lyme disease diagnosis is not a denial of patients symptoms and concerns, as being perceived as dismissive could further encourage patients' to pursue illegitimate therapies.

Finally, clinicians should guide these patients toward appropriate management of their complaints. This includes providing palliation of specific symptoms and conducting a thorough diagnostic work-up to determine the etiology of complaints, if one has not already been done. Some patients may also benefit from a psychiatric evaluation.

Conclusion

Patients with nonspecific symptoms ascribed to chronic Lyme disease pose special challenges and opportunities for physicians. When working with these patients, it is important to evaluate their complaints, perform laboratory tests, screen for tick exposure, and consider other disorders as well. Aspects of Lyme disease diagnosis and treatment should be clearly discussed, and patients should be directed toward legitimate sources of information. Prolonged or repeated courses of antibiotic therapy for these patients are ineffective and can put them at risk for dangerous complications. To avoid leaving patients who experience persistent symptoms feeling disregarded or alienated by mainstream medicine, their management should be approached in a collaborative, empathetic, and reassuring manner.

About the authors

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Case Study: A Patient Claiming Chronic Lyme Disease

A 47-year-old woman is referred to an infectious disease specialist by another practitioner for treatment of "chronic Lyme disease." The patient describes a 10-year history of severe insomnia that has worsened over the previous 8 months. She also complains of droopy eyelids, neck and

back stiffness, evanescent rashes, headache, blurry vision, difficulty concentrating, swollen glands, shortness of breath, chest pain, rib soreness, heart palpitations, upset stomach, irritable bladder, and auditory hallucinations.

She hands the specialist a 122-point checklist titled "Symptoms of Lyme Disease" and has checked 36 of the symptoms, encompassing every organ system. She requests treatment with 12 weeks of intravenous ceftriaxone.

The patient denies having spent time in wooded areas or being exposed to ticks. Her family history includes a sister who was diagnosed with chronic Lyme disease by a physician and treated with a prolonged course of ceftriaxone as well as a daughter who is ill with similar symptoms.

The woman's Lyme disease antibody test by EIA, which was ordered by her family physician and performed at a local reference laboratory, was negative (<0.99) at 0.33 units. Another sample sent to a reference laboratory that uses nonstandard methodology and interpretation showed 5 positive IgM bands on immunoblot, instead of the standard maximum of 3, and a single IgG band. This laboratory interpreted those results as positive for Lyme disease.

The patient recently had been given a 1-month course of 100 mg of doxycycline twice daily by her family physician, but her symptoms persisted. She had seen a neurologist and an ophthalmologist. Both reported normal examinations.

The infectious disease specialist's report describes a tired, anxious female with no rashes, adenopathy, cardiac irregularities, or focal neurologic signs noted by physical examination. The exam also shows no evidence of joint inflammation indicative of arthritis and no trigger point tenderness characteristic of fibromyalgia. Sedimentation rate and tests for lupus are negative. Her affect is subdued.

In evaluating the patient, the specialist faces a number of questions: Is this patient's history compatible with Lyme disease? Do her complaints warrant further antibiotic treatment? How can she be guided into proper care? Is chronic Lyme disease a valid diagnosis?

Chronic Lyme disease is not a valid diagnosis. In this case, some of the patient's subjective complaints may be compatible with late Lyme disease, but it is unlikely that Lyme disease is the cause of her symptoms. She lacks objective clinical findings and a history of tick exposure. Her IgG immunoblot, which one would expect to be positive in late Lyme disease, was negative because there were an insufficient number of bands. The positive IgM test alone does not warrant a Lyme disease diagnosis, since her symptoms have lasted for more than 30 days. Thus, she is not a candidate for antibiotic treatment for Lyme disease.

The patient suffers from myriad nonspecific symptoms referable to every organ system, and her exam and laboratory studies are normal. Therefore, her presentation is not suggestive of Lyme

disease, chronic fatigue syndrome, arthritis, or any other known medical illness. Because of this, the infectious disease specialist feels that a psychiatric disorder should be seriously considered.

How did the infectious disease specialist handle the situation? He started by explaining that, based on her laboratory tests and the lack of objective findings, he believed that she did not have chronic Lyme disease and was not a candidate for antibiotic therapy. He also discussed the risks associated with antibiotic therapy. Although some patients experience temporary improvement of symptoms with antibiotic treatment, the risk of serious adverse events, especially when antibiotics are administered by the parenteral route, outweighs any potential placebo or anti-inflammatory benefits. He then explained that her set of symptoms, in the context of her normal exam and laboratory studies, were not compatible with other known medical illnesses, and he gently recommended that the next step was to seek psychiatric care for her somatic symptoms.

The patient initially was resistant to the idea of a psychiatric referral and was angry that she would not receive intravenous antibiotics. Because the infectious disease specialist did not have the benefit of a long-term relationship with the patient, he conferred with the patient's primary care physician, who was able to convince her to undergo a psychiatric evaluation.

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