

## Lyme Disease: Beyond Erythema Migrans

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### Abstract

**Background:** With the recent discoveries of *Borrelia burgdorferi* and other spirochetes in the brains of Alzheimer's patients and with a recent analysis showing the very same pathology in both syphilitic and Alzheimer's dementia it seems both rational and urgent to consider all aspects of Lyme disease in a new light, especially the concept of "overdiagnosis". The very presence of the organisms in the brains following supposedly effective treatment for Lyme disease is contradictory and should be the starting point for diagnosis and treatment. Also for consideration is the reliance on erythema migrans and serologies in the diagnosis of Lyme disease inasmuch as they occur in less than half the patients.

**Keywords:** Lyme disease; *Borrelia burgdorferi*; Erythema migrans; Spirochetes; Arthritis; Neuroborreliosis

### Introduction

Lyme disease is a tick-borne infection causing major public health problems worldwide. Ixodes ticks, especially in their nymphal stage, are the transmitting agent of Lyme disease. A feeding tick, whose host is the white-tailed deer, must be attached for 24-48 hours before transmitting disease. Risk of infection after bite is 1%-3% [1-6]. In addition to their disease transmission, these ticks are thought to inject immunosuppressive, anticoagulant, and anti-inflammatory saliva into their hosts while feeding, allowing injected pathogens an opportunity to evade the immune system [7].

There are about 30,000 confirmed cases per year in the United States, but the Centers for Disease Control and Prevention recently estimates that the true number of cases may be 300,000 given under-reporting of the disease. This number may also be incorrect; a recent analysis reveals the "true" number may be 1 million in 8 nationwide surveys. In Maryland, an endemic region, the annual economic impact of chronic illness associated with Lyme disease is \$16,199 per patient [9]. It causes multi-organ infection with dermatological, rheumatological, neurological, and cardiac manifestations.

### Clinical manifestation

*Borrelia burgdorferi* is the primary etiologic agent of Lyme disease, and is a spirochete like *T. pallidum*. It is 10-30 microns in length (twice the size of the *syphilis spirochete*) and irregularly coiled [10] *B. afzelii*, and *B. garinii* are other less common causative species [11] that occur in Europe and are thought to be associated with *Borrelia* lymphocytoma and acrodermatitis chronica atrophicans, which are late cutaneous manifestations of Lyme disease [12]. Infection occurs in three stages, although infected patients may be asymptomatic. The gold standard of clinical diagnosis in early infection is the erythema (chronicum) migrans (EM) rash, which occurs in 80% of patients [13]. However, the true incidence of EM is unknown: it ranges from 27% to 40% to the 80% which is the CDC number [14,15]. One of the reasons

for this discrepancy is the multiple clinical presentations of EM: these include the classic "bull's eye", multiple lesions with dusky centers, red oval shaped plaque (cellulitis-like), an expanding rash with central clearing, a dusky blue-purple rash with no central clearing, and a red-blue lesion with central clearing. The "bull's eye", the one signature lesion of Lyme disease, is only one of many of the dermatologic findings [16]. The less familiar lesions may lead to marked under-reporting and under-recognition of this disease.

The EM "bull's-eye" lesion typically begins as a pink papule that expands centrifugally over days to become a plaque, classically with central clearing. *B. burgdorferi* organisms are found both in the center and periphery of erythema migrans rash. The largest diameter must be at least 5 cm. They are usually solitary but multiple EM-like lesions occur in up to 17% of patients. The rash may be accompanied by localized pain, localized pruritus, or lymphadenopathy but may also be asymptomatic. Stage 2 is early disseminated infection involving the nervous system, joints, and/or heart [17], and occurs within weeks of the rash. Weeks to months later, if left untreated, late disseminated infection occurs including persistent arthritis and acrodermatitis [13]. Involvement of the nervous system is termed neuroborreliosis [18] and is seen in up to 40% of infected individuals [18,19].

### Diagnosis

Per the Centers for Disease Control (CDC), confirmed cases may be [1] EM with a known tick exposure, [2] EM with laboratory evidence of infection and without a known tick exposure, or [3] at least one late manifestation of disease with laboratory evidence of infection. The CDC recommends serologic testing for Lyme disease follow a 2-test approach. The first step is an enzyme-linked immunosorbent assay (ELISA). If the initial ELISA is positive or equivocal, antibodies are tested, with positive result showing at least 2 of 5 and 5 of 10 bands for IgM and IgG, respectively. If symptoms have persisted <28 days, positive IgM or IgG are sufficient; if symptoms have been present >28 days, positive IgG is required [20]. In late or persistent infection, detection of antibodies to *B. burgdorferi* is highly specific and sensitive. Unfortunately, sensitivity of this testing in patients with early LD is only 29%-40% [21].

There are a growing number of cases of Lyme disease that do not meet the criteria set by the CDC which include erythema migrans, lymphocytic meningitis, Bell's palsy, arthritis, and heart block. This definition does not cover encephalopathy, polyneuropathy [22], neuropsychiatric disease, and chronic manifestations. Additionally, neither the ELISA testing nor the antibody testing is particularly sensitive. In a study of 46 patients with culture-proven erythema migrans, only 33% had a positive ELISA result and 43% had a positive IgM immunoblot. During follow-up, around 90% of the patients had IgG antibodies but using the IgG immunoblot criteria of the CDC showed a positive IgG in only 22% of patients [23].

The diagnostic gold standard is the isolation of *Borrelia* by culture with subsequent quantitative PCR (qPCR)-based confirmation. *Borrelia* can be cultured in 49% of skin biopsies of erythema migrans. Moreover, this method is not routinely used particularly since results are not available for 2-6 weeks, which is problematic because delay of treatment increases likelihood of long-term sequela of Lyme disease. Therefore, even when positive, this test is not useful for clinical decision-making.

*Borrelia burgdorferi* organisms can be detected in 80% of skin biopsy specimens by Qpcr [24]. Another study also confirmed that skin biopsy qPCR is positive (78%) in more samples than are culture positive (55%) [25]. In CSF testing for Lyme neuroborreliosis, qPCR for Borrelial DNA was detected in 15% of CSF samples [26]. In synovial fluid testing for Lyme arthritis, Borrelial DNA was detected in 85% of synovial fluid samples [27].

The C6 peptide reproduces the sequence of invariable region 6 in the variable surface antigen VlsE (Vmp-like sequence, expressed) of *B. burgdorferi*. Detection of IgM and IgG antibodies of C6 peptides using ELISA has a sensitivity of >70% for detecting Lyme disease. Pomelova et al showed that of their 146 Lyme disease patients, 51% had seroconversion of IgM antibodies, and 88% had seroconversion of IgG antibodies [28]. Liange et al showed that in acute infected patients, including early localized and early disseminated infection) sensitivity of the C6 ELISA was 74%. In late phase disease, sensitivity was 100%. In both cases, specificity was 99% [29]. Importantly, C6 peptide ELISA has no cross-reactivity with anti-recombinant outer surface protein A (OspA) antibodies, which can be seen in vaccinated patients [30].

### Evasion of immune system

Mechanisms of *B. burgdorferi* immune evasion, dormancy, and activation in hosts are best studied in the neurologic manifestations of *B. burgdorferi*. There are three recognized forms of neuropsychiatric disease in Lyme disease. The meningovascular form is associated with cerebrovascular infarcts [31,32]. The atrophic form is associated with cortical atrophy and gliosis, [31] and the central nervous form with neuropsychiatric symptoms [33]. It has been postulated that the pathophysiology of chronic Lyme disease involves a failure of the adaptive immune system leading to persistent infection by *B. burgdorferi*. Suggested mechanisms include deception of alternative complement pathway by surface antigens, dampening the plasminogen activation system, or continuously varying surface antigens [34]. In patient with neurologic manifestations of Lyme disease pro-inflammatory cytokines IL6 and TNF alpha are increased in the cerebrospinal fluid [35] and IL6 levels have been shown to correlate to disease activity in neuroborreliosis [36]. Additionally, the outer membrane of the Borrelial cell well expresses pro-inflammatory lipoproteins from the spirochetes [37]. These lipoproteins are up to 500-fold more active inducers of cytokines than lipoproteins of other

organisms including *Escherichia coli* [38] and can disseminate from the periphery to the brain [39].

### Treatment

When a patient presents with ring-shaped erythema that is consistent with erythema migrans and exposure in an endemic region, treatment is initiated. In cases with the rash is not classically consistent with EM, a non-endemic region warrants observation whereas an endemic region merits two-step ELISA [40].

Antibiotic efficacy against *B. burgdorferi* has been studied in vitro and in animal models. The generally accepted treatment for erythema migrans Lyme disease is a 14 day course of doxycycline. Prophylaxis with a single dose of 200 mg doxycycline after a tick bite was 87% effective in reducing erythema migrans in a randomized control trial [41]. However, caution must be used when providing prophylaxis as it could lead to a seronegative state that can delay diagnosis [42]. Amoxicillin is an alternative often used in children and pregnant women.

In beagle dogs infected by Ixodes ticks with confirmed positive skin cultures, spirochete levels were undetectable after treatment with either doxycycline or amoxicillin. However, skin biopsies taken from all antibiotic-treated dogs were PCR-positive for 23srRNA and ospA at one or more timepoints, indicating persistence of spirochetal DNA following antibiotic treatment [43]. In mice, low levels of spirochete DNA persisted in ceftriaxone-treated mice, although these mice did not have positive skin cultures or other evidence of disease [44]. In rhesus monkeys treated for chronic Lyme disease with 28 days of oral doxycycline, *Borrelia* antigen, DNA, and RNA were persistent after 90 days. Xenodiagnosis also recovered small numbers of intact spirochetes in treated monkeys [45].

This persistence of spirochetal DNA may be clinically significant. 34% of patients treated with a course of antibiotics had long-term sequelae of Lyme disease 6 years after treatment [46]. Asch et al conducted a retrospective cohort study of 215 patients diagnosed with Lyme disease based on the CDC criteria and followed the patients for 3.2 years. At follow-up, relapse with major organ involvement was seen in 28% of patient. 53% of the patient had "persistent symptoms of arthralgia, arthritis, cardiac, or neurologic involvement." Notably, however, antibiotic treatment initiated within 4 weeks of disease onset was more likely to result in complete recovery [47].

Persistent infection despite treatment is recognized as post-treatment Lyme disease syndrome (PTLDS). It is characterized by "fatigue, musculoskeletal pain, and cognitive complaints that persist for 6 months or longer after completion of antibiotic therapy" [48]. The primary identified risk factor is delayed diagnosis. These patients tend to show a low level of persistent anti-C6 titers compared to untreated patients who showed higher titers. The C6 antibodies occur on a region of the *B. burgdorferi* VlsE lipoprotein and are common to all infectious variants. Decline in the C6 antibody titer as measured by ELISA may serve as a predictor of treatment outcome [49]. There is evidence that *Borrelia burgdorferi* is capable of forming biofilm in vitro as it secretes extracellular polymeric substance which likely also contributes to its persistence despite treatment [50]. Further, there is evidence of spirochetal biofilm formation in the brains of Alzheimer's disease [51].

## Impact

Per the CDC, Lyme disease is likely much more common than reported. They estimate over 300,000 new cases each year in the United States alone. Insurance coverage of Lyme disease requires strict criteria. Both clinical diagnosis and fulfillment of CDC two-step diagnostic criteria is required. This is problematic because of the 40% sensitivity of the test. Many insurance companies specifically deny coverage of the more sensitive test - C6 peptide ELISA - due to "inadequate scientific evidence" [52]. Even when CDC criteria are met, antibiotics are covered for only 28 days, which has been shown to be too short a course to prevent long term sequela in about 28-34% of patients [46,47]. Furthermore because no randomized control trials have been performed for antibiotic use in post Lyme disease syndrome, additional antibiotic therapy in PTLDS patients is considered "experimental and investigational" [52]. Where the pathology of syphilis and Alzheimer's disease has been shown to be similar and where *Borrelia spirochetes* have been shown to be present in the brains of Alzheimer's disease, it seems no coincidence that patients with untreated syphilis have a 35% incidence of tertiary findings (including dementia) [53] and patients treated with doxycycline for Lyme disease have a 35% chance of tertiary disease. It seems as if treatment with doxycycline is like no treatment at all. Stricker and Johnson called for a "Manhattan Project" to combat the Lyme disease epidemic which causes untold suffering and which is many times more prevalent than HIV/AIDS [54]. Nothing less should be advocated in this scourge which represents failure on every level.

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