Modelling Late Disseminated Lyme Carditis

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Abstract

The development of Lyme disease-dilated cardiomyopathy likely involves three pathophysiological processes, including direct spirochetal invasion, dysfunctional immune response, and autoimmune processes. The association between Lyme disease and dilated cardiomyopathy remains tentative due to heterogenous results of existing studies. Further high-quality investigations are required to elucidate this potential link. Antibiotic therapy in patients with suspected Lyme disease-dilated cardiomyopathy may significantly improve clinical status and cardiac function, but its benefits are likely limited in late stages of the disease process.

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1 Introduction

Lyme disease (LD) progresses in discrete phases which are classically labeled as (i) early localized LD, (ii) early disseminated LD, and (iii) late disseminated LD. Lyme carditis (LC) is a well described cardiovascular phenomenon in early disseminated LD which is characterized by high-degree atrioventricular block (up to 10% of LC cases). Rarely, myocarditis and pericarditis may occur. However, the chronic sequalae of LC and its potential long-term consequences in late disseminated LD are poorly understood.

Late disseminated LD occurs months to years after initial infection [1]. One possible manifestation of late disseminated LC is dilated cardiomyopathy (DCM). DCM is characterized by left ventricular or biventricular enlargement, dilation, and impaired contractile function. This potential link was first identified by Stanek et al. in 1990 who described a case of a 54-year-old man with DCM and *B. burgdorferi* isolated on endomyocardial biopsy (EMB) [2].

Emerging literature continues to associate LD with the development of subsequent DCM. Accordingly, several case reports and observational studies have sparked further interest in this research area. However, this association remains controversial [3]. The aim of this chapter is to review the available literature on cardiac manifestations in late disseminated LD with commentary on pathophysiological processes, a review of the current literature, and future directions for research.

2 Pathophysiology

2.1 Pathogenesis of Cardiac Damage in *Borrelia* Infection

The mechanisms by which LD leads to cardiac damage have not been fully elucidated. Several have been postulated, including direct invasion of cardiac tissue by *B. burgdorferi*, immune evasion, dysfunctional immune response, and autoimmune processes resulting in chronic inflammation. A summary of the hypothesized pathophysiology of LD-DCM is provided in Fig. 1 [3].

B. burgdorferi evades both the innate and adaptive immune system by regulating the expression of its surface proteins. Examples in the outer surface protein E-related proteins and complement regulator-acquiring surface proteins. These proteins bind and inhibit C3b, which allows the spirochete to inactivate the complement cascade and resist complement-mediated killing. Further evasion of the host adaptive immune system and IgM-mediated killing in the early phase of infection

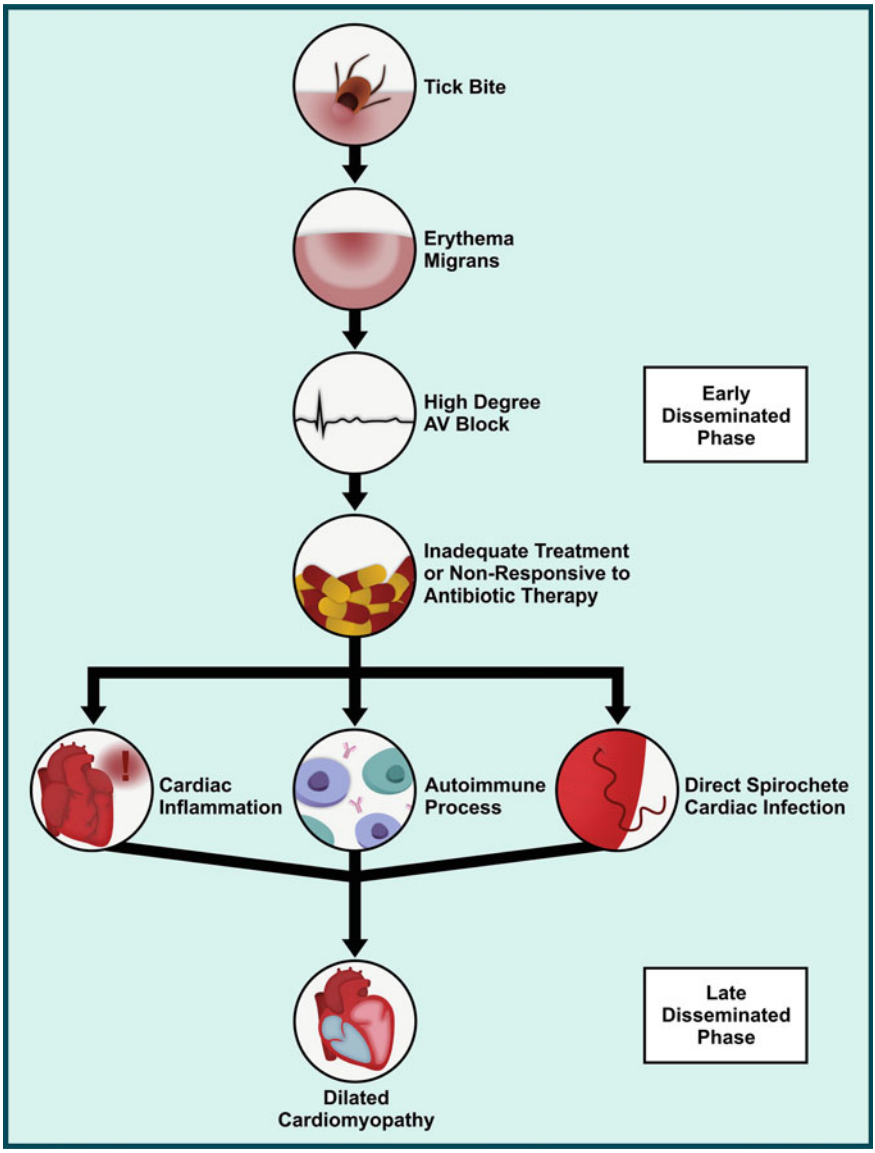

Fig. 1 Possible pathophysiological mechanisms involved in the development of LD-DCM. As a potential late manifestation of LD, LD-DCM may occur due to chronic inflammation, autoimmune processes, and direct spirochete infection of cardiac tissue

is facilitated by *Borrelia* decreasing the production of outer surface protein C and upregulating the expression of variable lipoprotein surface-exposed protein. What follows is an exaggerated and dysregulated immune response after myocardial colonization by the spirochete, leading to further cardiac damage [4].

Histologically, cardiac samples affected by suspected LD-DCM display transmural inflammation consisting of a band-like infiltration of macrophages and lymphocytes. Additionally, the presence of *Borrelia* has been identified in cardiac tissue. These findings are most often found in the connective tissue at the cardiac base, interventricular septum, and perivascular area. Histological examination of EMB samples from patients with suspected LD-DCM reveals a variety of abnormalities, including thickening and invasion of endomysial vessels by mononuclear cells, enlarged vesicular myonuclei, and atrophic and hypertrophic myocardial fibres [5]. Importantly, in some patients there is no evidence of cardiac inflammation, despite EMB culture growing *B. burgdorferi*, which suggests that LD-DCM may be caused by other processes. This is supported by research in a mouse model of LC, which demonstrated persistent residual lymphoplasmacytic infiltration even after heart inflammation subsided [6]. In the development of LD-DCM, chronic inflammation brought on by the presence of *Borrelia* or bacterial antigen in heart tissue may therefore play a significant role in its pathogenesis [7].

Murine models have shown that an autoimmune response can be triggered against cardiac tissue by IgM antibodies against *Borrelia* antigens. This may be due to a cross-reaction between *Borrelia* antigens and host cardiac proteins. ***Molecular mimicry*** is a form of autoimmunity in which there are structural similarities between foreign and self-antigens that stimulates the production of cross-reactive antibodies. This mechanism may also be involved in the pathogenesis of *Borrelia*-induced cardiomyopathy, as outer-surface protein A shares epitopes with cardiac myosin [8]. Antibodies directed against *Borrelia* may therefore react with cardiac myosin, suggesting that that persistent symptoms among some patients with underlying autoimmune disorders may not be caused by persistent infection.

Chronic inflammation triggered by the persistence of *Borrelia* or bacterial antigen in cardiac tissue may play a role in the development of LD-DCM. In one study of ten individuals with persistent DCM and suspected LD, histopathological investigation revealed myocyte hypertrophy, vacuolization, and interstitial fibrosis. Only a small minority fit the criteria for inflammatory DCM, indicating that chronic inflammation rather than acute myocarditis is more likely to be the cause of the findings. Notably, individuals with DCM who tested positive for *B. burgdorferi* had a greater incidence of autoimmune diseases. This is also consistent with research in murine models showing that autoimmune-susceptible animals had prolonged *B. burgdorferi* persistence in cardiac tissue. Although more research is needed to fully articulate the role of molecular mimicry in the development of LC, the presence of structural similarities between OspA and cardiac myosin is a hypothesis-generating finding [7].

Finally, it is important to consider patient risk factors and how they may mediate the risk of late cardiac manifestations of LD. These include pre-existing cardiac conditions, autoimmune conditions, and immunocompromise. Myocardial injury

is often followed by tissue necrosis and scar tissue development, a process partly regulated by the extracellular protein decorin. Decorin is upregulated to facilitate the remodelling process. *Borrelia* spirochetes adhere to the extracellular matrix via decorin-binding protein A on the spirochete's outer membrane in the disseminated phase of Lyme infection. Both decorin and decorin-binding protein A are necessary for cardiac infection by *Borrelia*, as demonstrated by reduced tropism to cardiac tissue in decorin knock-out mice [7]. It is therefore likely that multiple pathways are involved in the development of LD-DCM.

2.2 Lyme Persistence—Lessons Learned and Applied to Late Lyme Carditis

It has been well-demonstrated in several animal models and human studies that B. *burgdorferi* can survive the initial host immune response [9]. Research on primates has demonstrated that morphologically intact and metabolically active spirochetes in the brain and heart may endure antibiotic therapy. Patients who exhibit symptoms after appropriate therapy have raised suspicion that spirochetes may survive following treatment in humans. However, it remains unclear whether human patients who experience LD symptoms after antibiotic treatment still have an active infection. This is complicated by the lack of accurate diagnostic methods to detect whether infection has been eliminated in LD patients. Thus, it remains unknown to what extent ongoing infection, poor clearance of borrelial antigens, and/or autoimmune reactivity contribute to ongoing LD symptoms, including late cardiac manifestations.

It was initially thought that *B. burgdorferi* spirochetes isolated in patients treated appropriately with antibiotics were non-viable and therefore infection could not be persistent. This was based primarily on the fact that in LD, only *B. burgdorferi* genetic material, antigen, or non-culturable spirochetes have been detected following antibiotic treatment, with rare exception. However, evidence now exists that antibiotic-treated *B. burgdorferi* spirochetes can be persistent and, importantly, metabolically active [9]. *Borrelia* can alter its morphology to atypical dormant spirochete forms known as ***persisters*** in response to hostile environmental conditions [9]. Persisters can survive aggressive antibiotic therapy and transform into motile forms in favourable environments. Despite being non-culturable following antibiotic therapy, these persistent spirochetes retain the ability to alter the expression of bacterial genes in the infected host. These large-scale changes in gene expression include increased expression of pro-inflammatory cytokines and chemokines, as demonstrated in spirochetes localized to the dura mater of the brain. Persistent cystic forms of *B. burgdorferi* have been isolated from the cerebral cortex of patients with chronic Lyme neuroborreliosis, which may explain cases of persisting infection. One investigation on 33 patients with DCM identified spirochetes 10 patients on EMB analysis. Importantly, some of these spirochetes were identified in pleomorphic and atypical cystic forms, suggesting that persistent

Lyme infection of cardiac tissue may be involved in the pathogenesis of LD-DCM [10].

3 Overview of Evidence

3.1 Lyme and Dilated Cardiomyopathy—An Overview of the Literature

Eleven observational studies have been conducted thus far to try and explain the association between LD and DCM with heterogeneous results. All participants had pre-existing DCM. In line with the epidemiology of Lyme infection, the participants in these observational studies were usually more male than female, with mean ages ranging from 42 to 58 years. A recent systematic review has examined this relationship in detail [3].

All investigations implicating LD as a possible cause of DCM have been conducted among central European populations in endemic regions. Early reports relied primarily on seropositivity to make this association. In an Austrian study on patients with chronic idiopathic DCM, 19 of 72 were shown to be seropositive for IgG antibodies against *B. burgdorferi* compared to only seven patients of 55 with DCM due to coronary artery disease and five of 55 healthy control patients [11]. Several subsequent investigations from the same group found similar results, with one study finding 26% of patients (n = 46) with known idiopathic DCM being IgG seropositive against B. *burgdorferi* [12] and another finding nearly identical levels (24%) [13]. At least one of these patients had what appeared to be spirochete-like forms isolated from cardiac tissue. More recently, four observational studies utilized polymerase chain reaction (PCR) of EMB samples or peripheral PCR utilizing blood samples, as well as electron microscopy, to supplement serology findings. These investigations identified a significant prevalence of *B. burgdorferi* sensu lato genome in patients with suspected LD-DCM [5, 14–16]. In fact, one study detected *B. burgdorferi* sensu lato DNA in the EMB samples in all participants with DCM (n = 17). [14]

Studies conducted in the United States and United Kingdom have cast doubt on the association between LD and DCM. Four investigations, from both Europe and North America, have failed to show a connection between Lyme borreliosis and DCM. A study in an endemic region of the United States on 175 patients with DCM showed no significant difference in the seropositivity between patients with idiopathic DCM and ischemic DCM [17]. Similarly, in a study in the United Kingdom, although 8.2% of patients with DCM were seropositive against *B. burgdorferi*, this was not significantly greater than in the control groups. Additionally, immunoblot analysis was negative on all samples with positive enzyme-linked immunosorbent assay (ELISA) [18]. In one study in an endemic region of Germany, 12.5% of sera samples in patients with end-stage DCM were IgG-positive, which is not significantly higher than expected for populations in endemic regions for LD. Importantly, the *B. burgdorferi* OpsA gene was undetected in any patient

with DCM using a nested PCR technique [19]. More recently, a second German investigation examined the frequency of *B. burgdorferi*, *B. afzelii*, or *B. garinii* DNA in EMB samples from 64 patients with suspected inflammatory DCM who had positive *B. burgdorferi* IgM serology. PCR was used to identify *Borrelia* DNA in EMB samples, but found no evidence of the genomes of *B. burgdorferi*, *B. afzelii*, or *B. garinii* [20].

It is possible that *B. burgdorferi* only manifests in early stages of DCM and disappears from the myocardium over time. Further, in the absence of the active infectious agent, persistent post-inflammatory reactions generated by spirochetes may be the source of the cardiac structural and functional abnormalities seen in end-stage DCM. As all studies that did find a connection between LD and DCM were conducted in endemic areas of Europe, where B. *afzelii* and B. *garinii* are the common pathogens responsible for human LD, this discrepancy between the studies may also be explained by the geographical distribution of LD. *B. garinii* and *B. burgdorferi* appear to be more neurotropic and confers a stronger risk of neurological disease than *B. afezlii*. Infections with these strains are associated with different inflammatory profiles. For example, *B. burgdorferi* strains found in North America are associated with a T helper cell-1 adaptive immune response and elicit a higher level of cytokines and chemokines than their strains found in Europe [21]. It is unclear if these European strains produce a more indolent, subclinical infection that over a prolonged period could lead to the development of DCM. Additionally, *B burgdorferi* is not uniformly distributed in cardiac tissue. In murine models infected with *B. burgdorferi,* the spirochetes localized primarily to the cardiac apex. Therefore, samples might have been taken from regions devoid of B. *burgdorferi*. However, this remains speculative and the association between LD and DCM remains elusive.

3.2 Lyme Disease-Dilated Cardiomyopathy and Antibiotics

Perhaps the strongest evidence in support of an association between LD and the development of DCM is the improvement in cardiac function or the complete reversal of DCM with the administration of antibiotics. The majority of investigations to date have found that antibiotic treatment with or without conventional heart failure drugs significantly enhance cardiac function, reverses pathological cardiac remodelling, and improves clinical status [13, 15, 16, 20]. Conversely, two studies have found no improvement in left ventricular function or pathological remodeling after a standard course of ceftriaxone in patients with LD-DCM [5, 17].

How can we make sense of these contradictory findings? One hypothesis is that early antibiotic therapy in suspected LD-DCM could reduce inflammation prior to the development of permanent cardiac damage associated with chronic DCM. This is supported by a study that found a moderate correlation between the length of cardiac symptoms and improvement in cardiac function with antibiotics in eleven patients with *B. burgdorferi*-positive DCM. Patients with shorter DCM symptoms duration showed greater improvements in cardiac function [13]. It is therefore

possible that antibiotics in suspected LD-DCM may provide clinical benefits to patients only up until a certain point in the disease course.

3.3 Diagnostic Issues and Considerations

It is crucial to consider the difficulty of diagnosing LD in patients with idiopathic DCM when assessing the validity of the findings in studies investigating the link between LD and DCM. The existing literature on suspected LD-DCM has utilized several techniques to diagnose *Borrelia* infection. These includes ELISA alone, standard two-tier testing (STTT) (which combines ELISA with confirmatory immunoblotting), PCR (of blood and an EMB sample), and electron microscopy. Due to the low sensitivity of ELISA in the early stages of widespread LD and the post-treatment convalescent period, serological testing has been ineffective in establishing a causal relationship between LD and DCM. Additionally, it can be difficult to determine whether seropositivity is due to past or recent/current infection as both IgM and IgG *B. burgdorferi*-specific antibody response can last for years after the initial infection has been cleared. Other widely acknowledged limitations of serological testing include that these tests can cross-react with non-*B. burgdorferi* antibodies and their susceptibility to variable results depending on the choice of antigens used in the first-tier test, and their requirement for interpretation, particularly regarding the Western immunoblot assay, which may introduce bias. Therefore, the conclusions that can be drawn from the existing literature is limited and must be taken cautiously [3].

Although STTT is still the preferred diagnostic test, the absence of a standardized diagnostic methodology in the literature adds another layer of complexity when evaluating the relationship between LD and DCM. Recent investigations have employed the more sensitive approach of PCR testing and discovered a considerably greater incidence of *B. burgdorferi* in patients with DCM [5, 14–16, 19, 20]. This is due to the variable predictive value of ELISA serum assay and confirmatory immunoblotting. The *B. burgdorferi* genome was found in the myocardium of patients with presumably new onset DCM utilizing quantitative and qualitative PCR analysis and electron microscopy for direct spirochete detection. When compared to controls, the myocardium of DCM patients had a considerably higher rate of *B. burgdorferi* genome, according to quantitative PCR analysis of EMB samples [5].

One study found that a combination of western blot and qualitative serum PCR is the test with the greatest positive predictive value for *B. burgdorferi* sensu lato in EMB. Quantitative PCR was the gold standard for confirming *B. burgdorferi* in the endocardium, whereas a positive ELISA had just 50% sensitivity. *B. Burgdorferi* may become more closely associated to the development of DCM with the application of serum PCR and western blot [16]. However, due to the subpar assessment of PCR testing and electron microscopy in identifying *Borrelia* infection, these results should be regarded with care. As such, the International Diseases Society of America does not routinely recommend PCR testing of blood samples in

Table 1 Diagnostic methods utilized in investigations on suspected LD-DCM

Diagnostic method	Description	Advantages	Disadvantages
Standard two-tiered test	Consists of ELISA, which detects the presence of both IgM and IgG antibodies to *borrelia* Positive results are confirmed with immunoblotting	Cost-effective Readily available in most testing centers	Variable and generally poor sensitivity Difficult to determine whether seropositivity is due to recent/current or pre or recent/current infection
Polymerase chain reaction	Detects *borrelia* DNA in peripheral tissue (blood) or cardiac tissue	Cost-effective PCR can be used on a variety of testable tissue (e.g., blood, cerebrospinal fluid, cardiac tissue) The application of multiple PCR assays to the same sample can improve sensitivity	PCR for *B. burgdorferi* is not standardized. sensitivity varies according to the specific technique used The use of *B. burgdorferi* PCR directly on blood samples is substantially less sensitive compared with PCR performed on skin lesion samples in early infection Typically available only at large reference laboratories
Light microscopy	Quantitative method of detecting *borrelia* in cardiac tissue through use of microscopy	Allows for the direct detection of *borrelia*	Direct identification of spirochetes in tissue slides is limited due to low *borrelia* load Requires endomyocardial biopsy, which is invasive and rarely performed in clinical practice Heterogenous distribution of *borrelia* in cardiac tissue reduces sensitivity

patients with suspected LD. Diagnostic methods employed in suspected LD-DCM including their advantages and disadvantages are summarized in Table 1.

4 Future Directions and Conclusions

Several observational studies support the association between LD and DCM. Though, this relationship is not supported by randomized trials or definitive evidence of a pathophysiological relationship. Additionally, high quality studies are required to determine the most appropriate choice, route, and duration of antibiotic therapy in patients with suspected LD-DCM. Due to a lack of long-term follow-up research on LC patients or the possibility of patients receiving subpar LD treatment, the true prevalence of DCM in late disseminated LD may be underreported.

To assess if *B. burgdorferi* is a causal agent of DCM, whether antibiotic therapy would improve associated clinical outcomes, it is critical to perform large-scale longitudinal investigations and randomized controlled trials3].

Our understanding of the pathophysiology of LD-DCM remains poor and the relative importance of direct spirochetal infection, immune dysfunction, and autoimmune processes remains unclear. Preclinical investigations in murine models can help to better characterize how *Borrelia* invades cardiac tissue, promotes inflammation, and evades the immune system. Recently, the use of bioluminescent *Borrelia* has been employed to directly analyze the spatiotemporal expression and regulation of *Borrelia* genes, allowing for real-time evaluation of *Borrelia* load during murine infection. Analysis of the kinetics of infection of the different *Borrelia* genospecies and alterations in gene expression of *Borrelia* in cardiac tissue could be highly beneficial to our understanding of the pathophysiology of LD-DCM.

At present, clinicians may therefore rely on EMB, but this remains an invasive and potentially dangerous procedure that is not routinely used. Therefore, more investigations are required to identify biomarkers and unique features of LD-DCM to improve diagnostic accuracy and clinical management.

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