Cardiovascular manifestations of Lyme disease

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Lyme disease is caused by the treponema-like spirochete *Borrelia burgdorferi*.[1] Since Steere et al.[2] described the geographic clustering of cases in Lyme, Connecticut, over a decade ago, the disease has been recognized to be worldwide in distribution[3] and has become the leading tick-associated illness in North America and Europe.[4,5] Although Lyme disease is known to affect primarily the skin, heart, nervous system, and joints, the cardiac manifestations that occur in 4% to 10% of cases[5,6-8] remain the least well documented. The purpose of this report is to summarize the manifestations and management of cardiac involvement in Lyme disease.

HISTORICAL BACKGROUND

The characteristic cutaneous lesion of Lyme disease is *erythema migrans*.[9-11] While this lesion provided important clues about the cause of the illness,[11,12] it also linked Lyme disease in the United States with syndromes previously described in Europe.[13] It was the Swedish physician Arvid Afzelius who introduced the term *erythema migrans*, to designate a hitherto undescribed clinical entity, in a report to the Dermatological Society in Stockholm in 1909.[14] His observations were published later, in 1921.[15] Garin and Bujadoux[16] described a case of *erythema migrans* with meningopolyneuritis in 1922, and Hellerström[17] reported on an association between *erythema migrans* and meningoencephalitis in the following decade. In 1944, Bannwarth[18] defined a syndrome consisting of *erythema migrans*, radicular pain, and subsequently chronic lymphocytic meningitis, that still bears his name. Lennhoff,[19] in 1948, described spirochete-like structures in skin biopsies of erythematous lesions including *erythema migrans*. This led to the successful use of penicillin to treat both the *erythema migrans* as well as the associated central nervous system (CNS) involvement.[20-22]

Lyme disease was first recognized in epidemic form in Lyme, Connecticut, where a cluster of 59 cases appeared between 1974 and 1975. This "outbreak" was investigated, characterized, and described in 1977 by Steere et al.[2] at Yale University. The earliest cases of Lyme disease in the United States were traced retrospectively to Cape Cod in 1962, and to Lyme, Connecticut, in 1965,[23] and the first published case was reported from Wisconsin by Scrimenti[24] in 1970. The precise etiology of Lyme disease was not resolved until spirochetes were cultured from ticks by Burgdorfer et al.[1] in 1982, and later from the skin, blood, and spinal fluid of infected patients.[25,26]

MICROBIOLOGY

Along with the leptospira and treponema, borrelia species belong to the eubacterial phylum of spirochetes.[27] The biology of the borrelia species and of *B. burgdorferi* in particular has been reviewed elsewhere.[12,27,28] The geographic distribution of Lyme disease has been strongly correlated with the presence of hard-bodied ticks (Ixodidae), belonging to the *Ixodes ricinus* complex, which includes *I. ricinus*, *I. persulcatus*, *I. dammini*, *I. pacificus*, and *I. scapularis*.[3,29] The latter three species occur in North American woodlands where mammalian and avian hosts are abundant.[3,29]

Ticks are among the most efficient vectors of disease because they are persistent bloodsuckers, survive for 2 to 3 years, have few natural enemies, and have a high reproductive ability.[30] The pathophysiology of *B. burgdorferi* in Ixodid ticks has been well described.[31] In the Northeastern U.S., larvae and nymphs of *I. dammini* acquire *B. burgdorferi* when feeding from a variety of hosts, especially the white-footed mice.[25,32] Adults of *I. dammini* are prevalent during fall, winter, and spring and prefer the white-tailed deer as hosts.[30] Between hosts, ticks commonly inhabit tall grasslands and wooded areas where con-

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Table I. Stages of Lyme disease

Stage 1 (3 days—few weeks)
Begins with tick bite
Initially presents with *erythema migrans*
Generalized flu-like symptoms
Some are asymptomatic
Stage 2 (3 weeks—5 months)
Cardiac abnormalities in approximately 10% of documented cases
Neurologic abnormalities in approximately 11% of documented cases
Stage 3 (5 months—years)
Musculoskeletal involvement in approximately 50% of documented cases
Late neurologic manifestations
Limb numbness, memory lapses, and overpowering fatigue

tact with humans occurs.[30] The spirochetes are transmitted when the ticks refeed. About 90% of human cases occur between May and September when nymphal ticks are active, and it is this form that is most likely to bite humans.[33-36]

EPIDEMIOLOGY

Lyme disease is recognized globally, having been reported on five continents.[3, 23, 37, 38] Between 1983 and 1986, 5016 cases of Lyme disease were cataloged by the Center for Disease Control (CDC) in Atlanta.[5] With approximately 2000 cases per year now being reported in the U.S. from 43 states, Lyme disease has overtaken Rocky Mountain Spotted Fever to become the leading tick-associated illness in North America and Europe.[5, 39-42] Although prevalent throughout most of the country, 86% of U.S. cases were acquired in only seven states (Massachusetts, Rhode Island, Connecticut, New York, New Jersey, Wisconsin, and Minnesota).[5]

PATHOGENESIS

B. burgdorferi is either injected with tick saliva into the host skin or bloodstream, or in tick fecal material on host skin. Following a 3- to 32-day incubation period, the spirochetes are suspected to migrate outward in the skin. The primary *erythema migrans* lesion reflects the presence of organisms in the dermis with a perivascular infiltrate.[43, 44]

B. burgdorferi spreads through lymphatics (producing regional adenopathy) or enters the circulation via the skin vasculature. As the organisms disperse through the bloodstream, patients develop a systemic flu-like syndrome. In the acute spirochetemic phase, pathogens can disseminate to any organ (e.g., brain, heart, liver, spleen) or to other skin sites (secondary annular lesions).[45, 46]

CLINICAL PRESENTATION

Lyme disease is recognized as causing a wide spectrum of clinical illness. It has been traditionally divided into three stages (Table I). Stage 1 begins with the tick bite, which is only noted by a third of patients. This stage lasts between 3 days and a few weeks, averaging 7 days. The characteristic skin lesion of *erythema migrans* is seen in 30% to 90% of patients and usually fades after 3 to 4 weeks. There may be accompanying flu-like symptoms, such as fatigue, malaise, and lethargy in 80% of cases. Approximately 10% of patients are asymptomatic.[9, 12, 47, 48]

Stage 2 develops between 3 weeks and 5 months after disease onset, usually within the first 3 to 11 weeks. Approximately 10% of all patients in this stage develop cardiac abnormalities, and about 11% develop neurologic signs. Neurologic complications include headache, Bell's palsy, radiculoneuritis, transverse myelitis, meningitis, and encephalitis. Examination of the cerebrospinal fluid (CSF) is consistent with an aseptic meningitis.[9, 12, 47]

Stage 3 develops between 5 months to years after disease onset, but typically within 6 to 24 months. The most common feature is musculoskeletal involvement in up to 50% of patients. Large joints are commonly affected, usually as an asymmetric and monoarticular arthritis. Late neurologic manifestations involving demyelination with multiple sclerosis-like symptoms have been reported. Limb numbness, memory lapses, and overpowering fatigue may occur.[9, 12, 49] Also described are chronic encephalopathy, polyneuropathy, and rarely, leukoencephalitis.[50]

LABORATORY DIAGNOSIS

Definitive diagnosis of Lyme disease requires culture. Culture of blood and/or tissue is positive in 2-7% of patients with well-defined clinical illness.[25, 26, 51, 52] Because culture may require 4 to 12 weeks of incubation[53] and the yield is low, it is impractical for routine diagnostic use.

Laboratory diagnosis rests on serologic testing. Enzyme-linked immunosorbent assays (ELISA) and indirect immunofluorescent Ab (IFA)[48] identify 40% to 60% of patients in the first few weeks of infection when *erythema migrans* and constitutional symptoms predominate, and most patients with late complications.[54-57] In general, IgM Ab levels peak between the 3 to 6 weeks after clinical illness compared with IgG levels, which are detectable months to years later.[25] Theoretical improvements in early *B. burgdorferi* antibody detection have included the use of IgM capture ELISA and Western blots. The detection of five bands on an IgG or IgM immunoblot are

very significant, but there is no consensus on the specific combination of bands. The clinical value of urinary antigen and polymerase chain reaction technology needs further assessment.*

Dattwyler et al[61] studied 17 patients with acute Lyme disease who received prompt treatment with oral antibiotics. These patients developed chronic Lyme disease without diagnostic antibodies, as measured by ELISA, IFA, or Western blot. Diagnosis of *B. burgdorferi* exposure was based solely on the presence of T-cell lymphoproliferative responses. Although this technique of disease diagnosis is intriguing, Zoschke et al.[62] have questioned the specificity of lymphocyte proliferative responses because of the presence of reactivity in normal controls. Schutzer et al.[63] have also demonstrated the presence of *B. burgdorferi* antibody containing immune complexes in 10 seronegative patients with Lyme disease based on Western blot detection after immune complex dissociation. Thus seronegativity using current serologic techniques does not exclude the possibility of Lyme disease.

Pitfalls in the specific diagnosis relate to antigenic cross-reactivity among Borrelia species and between *B. burgdorferi* and *Treponema pallidum*. Patients with *B. burgdorferi* may develop positive treponemal tests for syphilis (e.g.: fluorescent treponemal antibody absorption [FTA-ABS], microhemagglutination assay for *T. pallidum* [MHA-TP]), but they generally do not develop positive non-treponemal tests (e.g.: venereal disease research laboratory [VDRL], rapid plasma reagin [RPR]). The clinical picture and the presence of a positive non-treponemal test may help differentiate syphilis from Lyme disease.[55,64]

Epidemiologic seroprevalence surveys have shown that many people with positive serology give no history of clinical illness.[43] Until the standardization and specificity of *B. burgdorferi* detection systems improve, definitive diagnosis in the absence of clear clinical syndromes will be problematic.[65]

CARDIAC MANIFESTATIONS

Cardiac involvement is the least well documented complication of Lyme disease, affecting 4% to 10% of all North American patients infected with *B. burgdorferi*[5,6,8,10] and 0.3% to 4.0% of all European patients with the disease.[66] Although *erythema migrans* appears to be more common in North America compared with Europe,[48,67] it has also been suggested that there may be differences between the virulence of European and North American *B. burgdorferi isolates*.[60,68,69]

*References 32, 45, 53, 54, 56, and 58 through 60.

Table II. Cardiac manifestations of Lyme disease

1. *Conduction system disease*
1°, 2°, 3° AV block
Wenckebach periodicity
Left bundle branch block
Right bundle branch block
Fluctuating bundle branch block
2. *Other cardiac disease*
Cardiomyopathy
Congestive heart failure
Myocarditis
Pericarditis
Atrial and ventricular tachycardias

Cardiac involvement usually occurs 4 to 8 weeks (range of 4 days to 7 months) after the initial illness.[5-7] Manifestations include rhythm disturbances, atrioventricular block, cardiomyopathy, heart failure, myocarditis, and pancarditis[70,71] (Table II). Of 84 patients with cardiac complications of Lyme disease reviewed by the Centers for Disease Control in Atlanta,[5] palpitations occurred in 69%, conduction defects occurred in 19%, myocarditis occurred in 10%, and left ventricular failure occurred in 5%. Overall, 21% of the patients required hospitalization.[5]

Conduction system disease. Atrioventricular block is the most common manifestation of Lyme carditis as well as the most troublesome.[70] In 52 cases reviewed by McAlister et al.,[7] 87% had documented atrioventricular block that was usually symptomatic. Up to 98% of patients with atrioventricular conduction disturbances demonstrated first-degree atrioventricular block at some time during their course. Wenckebach periodicity occurred in 40% and complete atrioventricular block occurred in 50% of patients. A temporary pacemaker was required in about 38% of affected individuals.[72] Individual patients may develop several types of atrioventricular block.[70]

Steere et al.[6] reported 20 patients with Lyme carditis, the largest single series in the literature. Ninety percent of these patients experienced fluctuating degrees of atrioventricular block, and 50% had high-grade atrioventricular block. Eight patients developed complete atrioventricular block and six required a temporary transvenous pacemaker for variable periods of time.[6] The most common clue to cardiac involvement was alternating tachycardia/bradycardia.[6]

Kimball et al.[73] described a patient presenting solely with complete heart block who came to medical attention because of the recent onset of easy fatigability and weakness. At the time of presentation,

Table III. Pathology of Lyme carditis

Transmural lymphoplasmacytic infiltrate
Inflammatory nodules of neutrophils and macrophages
Necrosis of myocardial fibers
Prominent interstitial fibrosis
Vasculitis of intramyocardial vessels
Fibrinous pericarditis
Presence of spirochetes in the myocardium

the patient lacked other signs or symptoms suggestive of Lyme disease, although he gave a history of previous rash.

Progression from first-degree to third-degree atrioventricular block can occur within minutes.[6, 74] Usually, block is at or above the atrioventricular node, predicting a benign prognosis.[6, 7, 9] Electrophysiologic studies have shown that atrioventricular block can occur at different levels within the atrioventricular conduction system. Sinoatrial and intraatrial conduction disturbances have also been described.[70]

More sinister conduction disturbances[7] include: (1) escape rhythms in some patients with severe atrioventricular block that are slow and of wide QRS pattern; (2) transient lack of any escape rhythm, with brief asystoles; and (3) fluctuating bundle branch block suggesting either transient His-Purkinje involvement or intranodal atrioventricular block. Electrophysiologic investigation of one patient with Lyme carditis demonstrated supra-Hisian block with complete absence of an escape mechanism. Rapid progression from 2:1 atrioventricular block to complete heart block was seen with subsidiary pacemaker failure, requiring insertion of a temporary transvenous pacemaker.[75-79]

Atrioventricular block frequently resolves gradually, usually within 6 weeks. Presumably this is related to resolution of the underlying inflammation. There may be a distinct progression from complete heart block through intervening degrees of heart block to first-degree atrioventricular block with a gradually decreasing PR interval, and ultimately back to normal sinus rhythm.[7, 74] The risk of developing complete atrioventricular block has been said to be higher in those patients who develop first-degree atrioventricular block with a PR interval greater than 0.3 second.[6, 7]

Other forms of cardiac involvement. In addition to conduction disturbances, *B. burgdorferi* can cause inflammation of all heart layers. Lorcerie et al.[80] described three patients whose only manifestation of Lyme disease was pericarditis with typical clinical features. *B. burgdorferi* was isolated from the myocardium of a patient with an unexplained dilated cardiomyopathy of 4 years' duration.[71] Diffuse T wave flattening or inversion, ST segment depression, transient and reversible depression of left ventricular function, cardiomegaly, and pericarditis have been noted in up to 65% of patients.[72] Other reports include evidence of congestive heart failure on chest x-ray examination, flow murmurs, mitral regurgitation murmurs, and various tachycardias including asymptomatic nonsustained ventricular tachycardia.[6, 70] These are nonspecific findings and it would be impossible to discriminate between chance associations and true signs of Lyme carditis.

Clinical investigation. Clinical investigative aids are insensitive and nonspecific in identifying Lyme carditis. The electrocardiogram may be normal or may identify any of the patterns previously described. The chest x-ray film is usually normal unless a cardiomyopathy or congestive heart failure is present.

Gallium-67 myocardial scanning has been documented by a number of authors[81-83] to show intense, diffuse uptake in the myocardium of at least some patients with Lyme carditis. This nonspecific test for inflammation may be used to assess for suspected cardiac involvement. Normalization of gallium uptake parallels resolution of Lyme carditis.

Pathology. The histology of Lyme carditis most commonly shows a transmural inflammatory infiltrate. The endocardial zone is affected by a characteristic band-like infiltrate of lymphoid cells. Small inflammatory nodules of neutrophils and macrophages are seen with hyperacute disease.[84] Isolated evidence of myocyte necrosis is sometimes seen. Endocardial and interstitial fibrosis may be prominent.[85] Spirochetes characteristic of *B. burgdorferi* can be found near and in the infiltrates, between muscle fibers, and in the endocardium[70, 86, 87] (Table III).

Inflammatory changes suggestive of a form of vasculitis may involve scattered small and large intramyocardial vessels. Swelling of endothelial cells is sometimes seen in small vessels, and this is associated with a tight perivascular response. Large vessels, by contrast, show adventitial infiltrates with loose reticulin and increased deposition of collagen.[84]

The findings in Lyme carditis differ from the histologic changes seen in other carditis entities. Rheumatic myocarditis is more focal and granulomatous. Bacterial myocarditis is often characterized by granulomatous infiltrates and neutrophils, or by lymphocytic infiltrates with small vessel vasculitis, as in infections by *T. pallidum*.[86, 87]

Other pathologic entities include myocarditis with early traces of myocardial fiber degeneration, and fibrinous pericarditis occurring in a patient with symptoms and signs of pericardial constriction.[86, 87] Fibrinous pericarditis is also described, with more dif-

fuse evidence of cardiac inflammation.[85] In one autopsy case, an additional finding of endodermal heterotopia ("mesothelioma") of the atrioventricular node was reported.[85] Although this was likely a coincidental finding, the possibility of this lesion being secondary to Lyme disease and accounting for the commonly seen conduction disturbances was raised.[85]

It appears that the presence of spirochetes in the myocardium is intrinsic to the pathophysiology of Lyme carditis. Whether continued disease activity requires the persistence of live spirochetes, or whether it results primarily from immune-mediated mechanisms is unclear. The discrepancy seen at histopathology between the small number of spirochetes recovered and the extent of the lymphoplasmacytic infiltrate suggests a combined effect of local spirochetal infection with an immunologic reaction to the infection.[86, 87]

Transvenous endomyocardial biopsy effectively aids in clinical diagnosis by revealing the band-like endocardial infiltrate. This is seen so often that the diagnosis of Lyme carditis is strongly suggested in an appropriate clinical setting, even if the quality of the endomyocardial biopsies is limited. If the biopsy includes underlying myocardial fibers, then the interstitial lymphoplasmacytic infiltrate will be seen.[84]

Prognosis. Although cardiac involvement in Lyme disease is generally benign, with most patients recovering without permanent sequelae, fatalities may occur. Marcus et al.[88] reported a 66-year-old man with babesiosis who died unexpectedly in the hospital. Autopsy showed pancarditis with a diffuse lymphoplasmacytic infiltrate and spirochetes in the myocardium. Antemortem sera were positive for *B. burgdorferi*. The authors concluded that the patient's sudden demise was likely due to atrioventricular block or to an arrhythmia. Their report has since been much quoted to suggest that cardiac involvement in Lyme disease could both be asymptomatic and yet not invariably benign. Since neither block nor arrhythmia was ever objectively demonstrated, this hypothesis cannot be considered conclusive and inferences regarding a cause and effect relationship should not be deduced from that report.

More recently, a fatal case of Lyme carditis occurring in an English farm worker has been reported.[85] Postmortem examination of the heart showed pericarditis, focal myocarditis, and prominent interstitial and endocardial fibrosis.[85]

THERAPY

Oral antibiotic therapy generally shortens the duration of *erythema migrans* and associated symptoms, while preventing or attenuating late illness in most patients.[12, 25, 89-92] Although antibiotic therapy in the early stages of Lyme disease has been reported to prevent or ameliorate later complications, its role in treating or preventing Lyme carditis has not been adequately assessed. It does not appear that early antibiotic therapy has decreased the duration of cardiac involvement, but formal testing of the effectiveness of antibiotic regimens in the treatment of Lyme carditis has not been possible, owing to the small number of cases.[67, 93-95]

Patients with minor cardiac involvement (i.e., first-degree atrioventricular block with PR interval less than 0.30 second) and no other symptoms should receive treatment with doxycycline, tetracycline, or amoxicillin as for early disease.[91, 92] Those with more severe conduction system disease (including first-degree atrioventricular block with a PR interval greater than 0.30 second) should be hospitalized and given either intravenous ceftriaxone or high-dose intravenous penicillin G.[91, 92, 96, 97] Advanced atrioventricular block is customarily treated with salicylates and steroids. One disadvantage to the use of steroids is that recurrent CNS and/or joint symptoms may be precipitated on steroid withdrawal. Therapy for 2 to 4 months before weaning is possible.[67, 98]

Asystole may be the major fatal complication of Lyme disease. Therefore telemetry in a coronary care unit (CCU) setting is advocated for patients presenting with second- or third-degree atrioventricular block, or for first-degree block with a PR interval greater than 0.3 second. Prompt insertion of a temporary transvenous pacemaker is suggested when aggravating features develop or when hemodynamic support is required.[95] Direct heart involvement is generally brief, and the pacemaker can usually be removed within a week.[7, 75, 99] Temporary cardiac pacing was used in 16 of 26 patients with high-grade or complete atrioventricular block reported in the literature. Nine patients with similar degrees of block were treated conservatively, some with atropine and/or isoproterenol.[7, 75, 99] Outcome did not differ between the groups. Chronic or irreversible atrioventricular conduction defects are being reported despite early and adequate antimicrobial therapy.[66] Serious atrioventricular conduction disturbances generally resolve within 2 to 6 weeks[72, 100, 101] but they may last 2 years[66] or even longer.[70] Permanent cardiac pacing has been reported in the setting of complete heart block secondary to Lyme carditis. In most instances, pacemakers were inserted prior to obtaining a firm diagnosis.[7, 102] However, permanent pacing was required in one patient whose complete atrioventricular block was refractory to aggressive pharmacologic therapy with antibiotics and steroids.[70]

SUMMARY

Although the cardiac manifestations of Lyme disease may be diverse, in general they are treatable with currently available therapies. A high index of suspicion is required to make a diagnosis, especially for patients who may lack a suggestive history of tick exposure or residence in an endemic region. Lyme disease-related heart block may require pacemaker insertion and supportive care. The efficacy of antibiotics in the therapy of acute and chronic cardiac Lyme disease will require further study. Serologic testing and cardiac histopathology are the most precise methods of diagnosis. There is a need to develop more sensitive and specific diagnostic tests for Lyme disease and for Lyme carditis in particular.

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