Lyme Disease

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Current Neurology and Neuroscience Reports 2002, **2:**479–487
Current Science Inc. ISSN 1528–4042
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Lyme disease is due to infection with a tick-borne spirochete, B*orrelia burgdorferi*. Risk for infection is confined to regions that contain the Ixodid tick vector. Characteristic skin, musculoskeletal, cardiac, ocular, and neurologic disorders are associated with the local, early dissemination and late stages of infection. Neurologic involvement can be seen at all stages, and involves both central and peripheral nervous system syndromes. The inability to easily culture *B. burgdorferi* and the lack of a reliable active infection assay have contributed to controversies in diagnosis and management. Because the vast majority of patients are seropositive, however, antibody testing is helpful to support the diagnosis of Lyme disease. With appropriate antibiotics, most patients do well. This infection provides an important model system to understand how interactions between an organism, vector, and host lead to disease. It also provides a model to study how infectious agents lead to neurologic disease.

Introduction

Lyme disease is a bacterial infection involving a tick-borne spirochete, *Borrelia burgdorferi*. It is the major vector-borne illness in the United States. Target body organs (skin, joints, heart, eyes, and nervous system) manifest characteristic syndromes. The inability to culture the organism easily had led to problematic issues in diagnosis and therapy. Accurate information about this interesting infection can guide appropriate evaluation and management strategies.

Epidemiology

Lyme disease is geographically restricted to regions with the tick vector. Infection is worldwide, reported from at least 50 countries on three continents (North America, Europe, Asia) [1–4]. The United States has three foci: Northeast coastal states (from Maine to Maryland), upper Midwest (Wisconsin and northern Minnesota), and Pacific West (northern California and Oregon). Although Lyme disease has been reported from 49 states, the enzootic cycle is documented in only a little over one third of states. Over 90% of cases come from nine states: Connecticut, Rhode Island, New York, Pennsylvania, Delaware, New Jersey, Maryland, Massachusetts, and Wisconsin. In Europe, Lyme disease occurs in forested regions, particularly within Sweden, Germany, Austria, and Slovenia. Approximately 50,000 cases occur annually [5].

In the United States, roughly 15,000 Lyme disease cases are reported to the Centers for Disease Control and Prevention (CDC) each year [6]. The prevalence rate of six per 100,000 is probably too low, because there is gross underreporting of the disease. Lyme disease has shown geographic spread. This may reflect ticks transported on mobile hosts, such as birds and racehorses, as well as new developments within wildlife regions. In highly endemic areas, 2% to 3% of the population develops Lyme disease. Asymptomatic infection rates are even higher.

Lyme disease presents from May through September in temperate climates, with peak cases in June and July. Although infection affects both sexes and all ages, children under the age of 15 years (25%) and middle-aged adults aged 30 to 59 years (45%) are particular targets. Time spent outdoors is the major risk factor, although infection can occur on brief trips to endemic areas, while mowing the lawn, or in the back yard.

Organism of Infection

Borrelia burgdorferi contains a protoplasmic cylinder, periplasm with motile flagella, and an outer membrane. It belongs to the *B. burgdorferi* sensu lato complex, which has at least 10 distinct genospecies. Three are pathogenic. *B. burgdorferi* sensu stricto is a virulent strain. It is found in North America and Europe and accounts for all Lyme disease in North America. *B. afzelii* is found in Europe and Asia and tends to cause milder disease with preferential dermatologic involvement. *B. garinii* is also found in Europe and Asia. This genospecies is particularly associated with neurologic disease.

The *B. burgdorferi* genome has been sequenced [7]. It consists of 1.5 megabases, with a single 950-kb linear chromosome, and nine linear and 12 circular plasmids. *B. burgdorferi* strains show considerable diversity with regard to gene and protein expression, and plasmids. There are over 100 spirochetal proteins. A number are not unique, leading to some degree of cross-reactivity.

Important proteins include the outer surface proteins (Osp) OspA through OspE, as well as VlsE. They are lipo-

Table 1. Clinical manifestations of Lyme disease

Infection	Exposure	System	Syndromes
Early local infection	0–30 d	Skin	Erythema migrans
Early disseminated infection	1–3 mo	Skin	Multifocal erythema migrans
			Lymphocytoma cutis (Europe)
		Heart	Heart block
		Musculoskeletal	Fluctuating arthralgias
		Nervous system	Meningitis, meningoencephalitis
			Cranial (especially facial) nerve palsy
			Acute painful radiculoneuritis
		Eye	Conjunctivitis
Late stage infection	>3 mo	Skin	Acrodermatitis chronica atrophicans (Europe)
		Musculoskeletal	Oligoarticular arthritis
		Nervous system	Chronic encephalopathy
			Chronic axonal radiculoneuropathy
			Chronic encephalomyelitis
		Eye	Uveitis

proteins coded by plasmid genes. Surface attachment proteins appear to be involved in determining disease virulence. *B. burgdorferi* relies on the host for nutritional support. Environmental factors affect gene and protein expression, which differs for spirochetes in the tick vector, the human host, or the test tube [8,9]. As the tick feeds on a host, exposure to blood leads to an explosive growth in spirochete numbers, down-regulation of OspA and up-regulation of OspC, and migration of spirochetes from the tick gut to the salivary glands. Organisms are then inoculated into the host via saliva of the feeding tick.

Vector of Infection

Borrelia burgdorferi infects hard body ticks of the *Ixodes ricinus* complex. They are very small and easy to miss. There is a 2-year life cycle with three stages (larva, nymph, adult) and three blood meals. The bite is typically painless. Ticks will stay attached for days, becoming engorged with blood. In the United States, *I. scapularis* (*I. dammini*) is the vector in the Northeast and Midwest, whereas *I. pacificus* is the vector in the West. *I. scapularis* is also found in the South, but has a much lower rate of infection than northern ticks. In Europe *I. ricinus* is the vector, whereas in Eastern Europe and Asia the vector is *I. persulcatus*.

The questing nymph, which feeds in late spring and early summer, is most likely to bite humans. Virtually all cases of Lyme disease involve tick bite. There are rare congenital transmissions, but this is very uncommon [2,10•]. Because there is little transovarial passage of *Borrelia burgdorferi*, ticks are often infected by feeding on spirochemic hosts.

Hosts

Ixodid ticks can feed on over 100 distinct hosts, including birds, mammals, and small vertebrates. Humans are uncommon accidental hosts. The preferred host depends on the tick strain, stage, and geographic location. *Ixodes scapularis* larval and nymphal ticks prefer to feed on the wild white-footed mouse, which remains healthy despite prolonged spirochetemia and, therefore, can transmit spirochetes to uninfected ticks. Adult *I. scapularis* ticks prefer the white-tailed deer. A preferred host for *I. scapularis* in the South, as well as *I. pacificus* in the East, is a lizard, which is a nonamplifying host [4]. This feature contributes to the lower infection rate in these regions.

Clinical Manifestations

Borrelia burgdorferi infection may be asymptomatic. The proportion of patients with subclinical infection is not known, but approximates 20%. Like other human spirochetal infections (syphilis, leptospirosis, relapsing fever), clinical disease occurs in stages punctuated by relatively silent periods. Following local infection at the inoculation site, there is dissemination via blood and possibly lymphatics and skin. Even during early local infection, blood dissemination has occurred in at least 50% of patients [11]. Organisms may then remain within infected organs to cause late disease.

Clinical manifestations of Lyme disease can be divided into characteristic syndromes associated with early local, early disseminated, and late stage infection (Table 1).

Erythema migrans (EM) occurs in 90% of diagnoses of Lyme disease cases. An expanding red macule or papule occurs at the site of the tick bite 1 to 30 (typically 7 to 10) days after spirochetes are inoculated into skin. Lesions that appear within 24 hours of tick bite reflect hypersensitivity reactions, whereas lesions that clear within 48 hours are not consistent with EM. The key lesion feature is expansion over time, and EM can become quite large. Although the classic description is a large, painless bull's eye rash, there are many atypical variations with small, irregular, raised vesicular or pruritic lesions. EM is the only pathognomic clinical marker of Lyme disease. It represents early local infection. Flu-like illness during summer has also been associated with seroconversion.

Multiple EM lesions indicate dissemination. Two unusual skin manifestations have been reported from Europe. Lymphocytoma cutis involves inflammatory nodules containing plasma cells that affect the nipple or earlobe [12]. Acrodermatitis chronica atrophicans (associated with *B. afzelii*) occurs most often on sun-exposed sites on the lower legs, affects elderly women, and is associated with a predominantly sensory polyneuropathy in at least one third of patients. Spirochetes have been cultured from skin up to a decade after initial infection.

Musculoskeletal involvement involves migratory nonspecific arthralgias and myalgias in the early dissemination phase, and tenosynovitis (episodic painless swelling of large joints) in the late stage. Joint involvement occurs in up to 60% of late infections. The knee is most commonly involved, sometimes associated with Baker's cyst. Temporomandibular joint involvement is particularly suggestive.

Cardiac involvement during dissemination is unusual (5% of cases). High-grade fluctuating atrioventricular heart block is the most suggestive syndrome, but there have been cases of acute myopericarditis, cardiomegaly, mild left ventricular dysfunction, fatal pancarditis, and chronic dilated cardiomyopathy (in Europe).

Conjunctivitis can be seen during acute dissemination syndromes. Less well documented are occasional cases of uveitis reported as late infection manifestations.

Neurologic Manifestations

The nervous system is a favored target in Lyme disease, with both central (CNS) and peripheral nervous system (PNS) syndromes associated with the disseminated and late stages of infection (Table 1) [13•]. The CNS can even be involved during local infection, reflecting premeningitic seeding.

The neurologic syndromes of Lyme disease are often accompanied by a subjective multisymptom complex (various combinations of arthralgias, myalgias, fatigue, cognitive complaints, stiff neck, headache, paresthesias, and palpitations). Symptoms tend to be more severe with early dissemination syndromes. The most common, Lyme meningitis, mimics aseptic viral meningitis. Headache ranges from quite mild to fairly severe, but meningismus is often subtle. Meningitis may occur with associated facial nerve or radicular involvement, a very suggestive pattern for Lyme disease.

Isolated cranial nerve palsy, another early dissemination syndrome, invariably involves the facial nerve. Unlike Bell's palsy, patients with Lyme-related facial nerve palsy usually have a multisymptom complex and may even have simultaneous EM. In one third of cases, there is bilateral facial nerve involvement. The second nerve may be affected during recovery. In rare cases, other cranial nerves (III, IV, VI, V, VIII) may be involved. For example, sudden sensorineural hearing loss can occur [14]. Although optic nerve involvement is reported, documentation is not strong and this is probably extremely rare.

The third dissemination syndrome, acute painful radiculoneuritis, is also called painful lymphocytic meningoradiculitis (Bannwarth's syndrome) in Europe. This syndrome has the most inflammatory cerebrospinal fluid (CSF) changes. Meningitis symptoms (headache, stiff neck) are very subtle, whereas dermatomal/myotomal features and lancinating intrascapular or extremity pains may be striking. Permanent deficits can include scapular winging. This is the most common manifestation of neurologic Lyme disease in Europe, but is quite unusual in North America.

Among late-infection neurologic syndromes, the most common in North America is a subtle encephalopathy that most likely reflects CNS infection [15,16]. Patients are functional, but experience memory problems, concentration difficulties, and attention and mental processing deficits. A second syndrome, chronic axonal polyradiculoneuropathy, is now uncommon. Patients note subtle paresthesias or rare radicular pains, and electrodiagnostic testing documents multifocal involvement. This late PNS syndrome often accompanies encephalopathy. Chronic Lyme encephalitis/encephalomyelitis is rare. There is parenchymal involvement, which can suggest a variety of disorders (brain tumor, multiple sclerosis, movement disorders). Virtually all chronic encephalomyelitis cases come from Europe.

These six syndromes are the most suggestive for Lyme disease. Other reported neurologic manifestations include an intracranial hypertension syndrome, which seems to be age specific (children and adolescents). It is associated with CSF abnormalities, but not obesity or female sex. Lyme disease has caused cerebellar and vascular syndromes (stroke, vasculitis, transient ischemic attack, hemorrhage), transverse myelitis, dementia syndromes, and even rare cases mimicking motor neuron disease and Guillain-Barré syndrome [17–19].

Diagnosis

A major issue for diagnosis is that *B. burgdorferi* is extremely difficult to culture. Culture requires special medium, takes weeks, and must be performed in laboratories with a specialized interest in the disease. It is most likely to be positive in skin punch biopsy, performed at the leading edge of an EM lesion, because skin is teaming with organisms. This is almost never necessary to diagnose EM, however. Even during the early dissemination phase, a large volume of plasma is needed to produce positive cultures in about half of cases [11]. Yield of culture is so poor that it is not routinely recommended.

Lyme disease is a clinical diagnosis, but should be supported by laboratory data to minimize misdiagnosis (Table 2). The one exception is a diagnosis of EM, which requires no ancillary laboratory testing. The CDC surveillance criteria are quite strict. They are used for epidemiologic studies or formal studies, but are not used clinically. The American Academy of Neurology (AAN) practice guidelines specify suggestive neurologic abnormalities, mandate other

Table 2. Diagnosis of Lyme disease including neurologic infection

Centers for Disease Control case definition (national surveillance criteria)
Erythema migrans (physician documented)
Lesion must reach at least 5 cm
Suggestive clinical syndrome supported by laboratory data
Neurologic syndromes (meningitis, cranial neuritis, radiculoneuropathy, encephalomyelitis with intrathecal antibody production)
Cardiac syndromes (acute second/third degree heart block)
Musculoskeletal syndrome (recurrent, brief swollen joints)
Laboratory evidence (isolation of *Borrelia burgdorferi* from tissue or body fluids, or detection of diagnostic antibody levels using two-tier CDC system)
American Academy of Neurology guidelines
Exposure to appropriate ticks in Lyme-endemic region
One or more of these criteria
Skin manifestation (erythema migrans or histologically proven lymphocytoma cutis, acrodermatitis chronic atrophicans)
Immunologic evidence of *B. burgdorferi* exposure
Detectable *B. burgdorferi* (by culture, histology, or polymerase chain reaction test)
One or more specified disorders, no other etiology, possible additional testing such as CSF studies
Causally related disease
Lymphocytic meningitis ± cranial neuropathy, painful radiculoneuritis, or both
Encephalomyelitis
Peripheral neuropathy
Causally related syndrome
Encephalopathy
Diagnostic clues for neurologic Lyme disease
Historical clues
Endemic area exposure (with outdoor activities)
Ixodid tick exposure or bite
Suggestive rash or flu-like illness preceeding neurologic disease
Suggestive neurologic syndrome
Accompanying multisymptom complex
Examination clues for neurologic Lyme disease
Extraneural involvement
Unilateral/bilateral facial nerve palsy
Laboratory clues for neurologic Lyme disease
Anti-*B. burgdorferi* antibodies
Acute phase reactants, liver enzymes (increased in early infection)
Anticardiolipin immunoglobulin G antibodies
CSF (intrathecal anti-*B. burgdorferi* antibody protection, mononuclear pleocytosis, increased protein)
Nerve conduction tests, electromyography (axonal radiculoneuropathy)
Brain single photon emission computed tomography
Neurocognitive testing
Electrocardiogram (conduction block)

CDC—Centers for Disease Control; CSF—cerebrospinal fluid.

conditions be ruled out, and require supportive laboratory data or prior pathognomic skin involvement [20].

The most useful laboratory diagnostic test is positive serology. The CDC recommends a two-tier test system. Most screening tests involve enzyme-linked immunosorbent assays (ELISA) that use whole *B. burgdorferi* sonicate as the antigen target. First-tier tests are not standardized. They can use different antigen preparations, test parameters, controls, and assay cutoffs, and often show inconsistency. When the first-tier test shows a borderline or positive reaction, it is routinely confirmed by the more specific second-tier Western immunoblot assay. This test is standardized to the extent that a positive immunoglobulin M (IgM) immunoblot requires staining for two of three specified (23, 39, 41 kD) bands, and a positive IgG immunoblot requires staining for five of 10 specified (18, 23, 28, 30, 39, 41, 45, 58, 66, 93 kD) bands. However, immunoblot assays are not standardized for target antigen, use of recombinant proteins and monoclonal antibody controls, or assay specifics. A positive result is a subjective, qualitative determination. The IgM immunoblot is not recommended for use in clinical syndromes longer than 1 to 2 months in duration, because positives are more likely to reflect false-positive results.

First-generation serologic tests have a minimum false-positive rate of 5%, because a number of immunodominant antigens are not unique to *B. burgdorferi*. In particular, strong humoral responses to the p41 flagellin and a variety of heat

shock proteins may be induced by other processes. Other spirochetal infections and autoimmune disorders can give false-positive results. Dental procedures or gum disease can result in false-positive serology from cross-reactive *Treponema denticola* mouth flora spirochetes. In one study, low-positive Lyme ELISA occurred in up to one third of endemic-area healthy subjects and other neurologic disease control subjects [21]. Most Lyme disease cases produce positive ELISA results, so it is the borderline or low-positive results that are most likely to be false positives. In recent years, there has been an attempt to discourage routine Lyme serology testing unless there is a serious consideration of infection.

Although seronegative Lyme disease does occur, it probably accounts for less than 10% of cases. Early antibiotics can interfere with the normal humoral response. Only half of EM patients are seropositive, because it takes 2 weeks for detectable IgM antibodies by Western immunoblot. In culture-proven EM patients who receive treatment, about 20% never seroconvert.

Unfortunately, no active infection assays are routinely available. A Lyme urine antigen test (LUAT) is offered commercially, but gives inconsistent results and should not be used [22]. Polymerase chain reaction (PCR), if done in a reliable laboratory to minimize false-positive reactions, shows a high yield on skin punch biopsy samples and synovial fluid [23]. It is relatively insensitive in CSF, and less than 40% of neurologic Lyme cases show a positive PCR reaction [24]. This undoubtedly reflects the tissue tropism of *Borrelia burgdorferi*, with very few spirochetes floating free in the CSF. PCR positivity is improved by pelleting CSF.

For neurologic Lyme disease, CSF is helpful to confirm CNS involvement. Paired CSF-serum antibody analysis, to measure intrathecal anti-*B. burgdorferi* antibody production, is the most useful test. It provides strong indirect evidence for CNS infection. There are rare reports of false-positive results in disorders such as tuberculous meningitis and *Varicella zoster* virus meningoencephalitis. Intrathecal antibody production can also remain positive for months to years, so it is not a useful measure to follow treatment response. The same is true for serum antibody titers. Nonspecific but suggestive CSF abnormalities include mononuclear pleocytosis and increased protein. A recent study suggests a distinctive CSF matrix metalloproteinase pattern (MMP), with 130 kD MMP without 92 kD MMP [25]. In North America, oligoclonal bands (OCB) and intrathecal (total) IgG production (usually an elevated IgG index) are uncommon. Even intrathecal anti-*Borrelia burgdorferi* antibody production, which is most often noted in meningitis and acute radiculoneuritis cases, does not have to be positive in neurologic Lyme disease. In contrast, all neurologic infections in Europe show intrathecal anti-*B. burgdorferi* antibody production, positive OCB, and elevated IgG index. This probably reflects genospecies and strain differences, with a more inflammatory intrathecal response from European strains.

New Serologic Testing

There are a number of second-generation antibody tests. One uses recombinant chimeric Borrelia proteins (containing immunodominant epitopes of several antigens) in a rapid (20 minute) point of service test [26]. Another is the C6 *B. burgdorferi* ELISA kit (Immunogenics, Cambridge, MA), which uses as target antigen a 26-amino acid sequence from a unique surface protein, VlsE [27]. There are also automated immunoblot assays that use recombinant proteins [28]. These second-generation tests have not yet been adopted widely, but are likely to improve diagnosis by decreasing false-positive reactions. Several groups are also investigating detection of antibody within circulating immune complexes as a way to document active infection [29–31].

Treatment

Lyme disease responds to appropriate antibiotics, but the earlier patients are treated the better. The Infectious Disease Society of America (IDSA) provides guidelines that recommend early local or disseminated infections be treated with oral doxycycline (100 mg twice a day) or amoxicillin (500 mg three times a day) for 14 to 21 days [11]. In allergic patients, cefuroxime axetil (500 mg twice a day) or erythromycin (250 mg four times a day) can be used. They recommend that neurologic disease be treated with intravenous (IV) ceftriaxone (2 g once a day), cefotaxime (2 g three times a day), or penicillin (3.3 million units every 4 hours). Allergic patients can be treated with doxycycline, 100 mg three times a day for 30 days. Although the IDSA guidelines state that facial nerve palsy may be treated with oral regimens, this is probably not wise in light of the fact that most such cases reflect CNS infection with abnormal CSF [7,15,32,33]. There are also examples of neurologic disease after a month of oral antibiotics. The IDSA guidelines recommend Lyme arthritis be treated with 1 to 2 months of oral therapy, or 14 to 21 days of IV therapy, and that Lyme carditis be treated with 14 to 21 days of oral therapy (for first degree block), or with IV regimens and cardiac monitoring (for high-degree heart block).

Ceftriaxione is the preferred treatment for neurologic Lyme disease (Table 3) [34]. It is given once a day, typically delivered over 30 minutes by way of a peripherally inserted central catheter (PICC) line, for 4 weeks. This line can be used for several weeks. This third-generation cephalosporin shows good serum levels, penetrates into CSF and body organs, and is well tolerated. It can wipe out normal bowel flora, leading to *Clostridium dificile* colitis. This risk can be minimized by using acidophilus (*Lactobacillus* species), which can be obtained from health food stores [35]. One to 10 billion viable organisms are taken daily, divided over a schedule of three to four times a day. Another caution is that ceftriaxone promotes biliary sludge, and young women and children who are treated over many weeks

Table 3. Practical treatment guidelines for Lyme disease

Erythema migrans treatment (oral)
Doxycycline, 100 mg twice a day for 14–21 d
Amoxicillin, 500 mg three times a day (children: 250 mg three times a day, or 50 mg/kg/d divided three times a day)
Cefuroxime axetil, 500 mg twice a day
Neurologic disease (intravenous)
Ceftriaxone, 2 g once a day for 4 wk; may extend to 6–8 wk for severe parenchymal involvement (children: 75–100 mg/kg/d to maximum of 2 g)
Cefotaxime, 2 g every 8 h (children: 150 mg/kg/d divided three to four times a day)
Doxycycline, 200 mg twice a day (oral or intravenous)
Penicillin G, 3–4 million U every 4 h (20 million U/d) (children: 200,000–400,000 U/kg/d in 6 divided doses)

seem particularly vulnerable to biliary cholelithiasis. Whenever an in-dwelling line is used to deliver antibiotics, there is risk of it being infected. In general, however, treatment over 1 month is well tolerated. Cefotaxime is an alternate third-generation cephalosporin, but its dosing schedule is not as convenient.

Pregnant patients can be treated with either amoxicillin or ceftriaxone. Doxycycline is not used during pregnancy or in children under 8 years of age because of bone problems and tooth discoloration.

Prevention

Prevention is optimal treatment of infection. Strategies include avoidance of tick-infected habitat, use of personal protective strategies, reduction of tick populations, regular body checks to remove attached ticks, and chemoprophylaxis of tick bite. Two studies suggest that exposure to mouse-favorable niches is minimized by avoiding areas where the vegetation is above ankle height and there is no visible bare ground [36,37]. Ticks must feed for a prolonged period of time to transmit *Borrelia burgdorferi*, at least 24 hours and possibly as long as 72 hours [38]. Therefore, daily checks to remove attached ticks can avoid infection. Ticks become engorged when they have been feeding for a prolonged period, so that an attached but nonengorged tick has not transmitted infection. After tick bite, chemoprophylaxis within 72 hours with a single oral dose of doxycycline (200 mg) is 87% effective in preventing Lyme disease [39]. In a study of 482 patients bitten by an Ixodid tick, EM developed in one of 235 patients randomized to doxycycline compared with eight of 247 patients (3.2%) who received placebo. No asymptomatic seroconversions were noted. Risk of EM was highest when the bite involved an engorged nymphal tick.

Definitive prevention involves immunoprophylaxis. The LYMErix vaccine (GlaxoSmithKline Biologics, Research Triangle Park, NC) is a noninfectious recombinant vaccine consisting of 30 μg of OspA plus 0.5 mg of aluminum hydroxide adjuvant. In a large clinical trial that involved thousands of patients, protection was 49% after two doses and 76% after three doses [40]. The vaccine was approved for a three-schedule (0, 1, and 12 months) intramuscular injection in 1999. Unfortunately, the vaccine was removed from the market after three seasons of use because of disappointing sales. The market for this vaccine is limited [41•]. Use had been clouded by concerns about using OspA as an immunizing antigen because of the possibility of inducing arthritis (see following section). Certain vaccinated individuals also reported development of a chronic pain syndrome after being vaccinated. Despite the disappointing market, other Lyme vaccines, including multivalent products, continue to be developed. Particularly promising are anti-tick vaccines, which ostensibly would protect against all tick pathogens.

Pathogenesis

Lyme disease is associated with a diverse array of clinical syndromes, yet pathologic studies do not suggest significant tissue damage. Spirochete numbers are also quite limited. Both spirochete and host properties likely play a role in disease pathogenesis (Table 4) [13•].

An important feature is the immune activation produced by *B. burgdorferi* components (including lipoproteins) that activate T and B cells, and induce proinflammatory cytokine production [43]. Limited neuropathologic studies indicate little tissue destruction. CNS tissue shows microglial nodules, meningeal and perivascular inflammation that includes CD4+ T cells, mild spongiform changes, and rare extracellular spirochetes. In very unusual cases, there is obliterative vasculopathy, demyelination, or granulomatous changes. PNS tissue shows axon damage, with epineural, perineural, and perivascular inflammation, and angiopathy within the vasa nervorum. Skeletal muscle has shown focal myositis, interstitial inflammation, occasional focal necrosis, and rare spirochetes within muscle. With the exception of a report of spirochetal DNA (detected by PCR) in a sural nerve biopsy, spirochetes have not been reported within damaged peripheral nerve tissue [44]. Pathologic studies of joint tissue are more readily available. Lyme arthritis is associated with mononuclear inflammation, vascular proliferation, and synovial hypertrophy with γ δ T cells and *B. burgdorferi*-reactive TH1 lymphocytes. The syndrome of chronic Lyme arthritis, which accounts for 10% of Lyme arthritis cases, appears to be immune mediated, rather than infectious, in nature. Patients do not respond to antibiotics and do not have PCR-positive synovial fluid. Human lymphocyte antigen (HLA)-DR4–positive individuals are particularly susceptible. Chronic Lyme arthritis patients show a strong immune response to OspA, with reactive lymphocytes and high antibody titers. Involved joints have high levels of anti-OspA antibodies in synovial fluid, CD4+T cells reac-

Table 4. Pathogenesis factors in Lyme disease

Spirochete properties
Spirochetes produce varying degrees of vasculopathy
Organisms are sparse, extracellular, and associated with collagen fibers during host infection
Spirochetes can remain quiescent for years, with intermittent reactivations and episodic clinical disease
Spirochete components activate the immune system, and produce inflammation out of proportion to number of organisms
Spirochetes show molecular mimicry with human antigens (for example, OspA cross-reacts with human lymphocyte functional antigen-1)
Distinct *Borrelia burgdorferi* genospecies and strains predispose to specific clinical disease patterns
Host properties
The humoral immune response is important to clear infection
Certain immune responses correlate with disease
Chronic Lyme arthritis is associated with strong OspA and OspB antibody responses, whereas mild, self-limited arthritis is associated with a p35 response [6,42]

Osp—outer surface protein.

tive to OspA, and elevated levels of proinflammatory cytokines. There is also up-regulation of synovial adhesion molecule expression [2,45].

Animal models of Lyme disease, which can be produced in multiple species, indicate infection is a multifactorial process. Disease severity is determined not only by the number of organisms and strain virulence, but also by the host genotype and immune response. The rhesus primate model best mimics neurologic disease [47–49]. In this model, CNS and PNS involvement are noted in both the acute and chronic phases of infection. Inflammation remains limited despite ongoing infection. Similar to humans, culture positivity of neural tissue is rare, and PCR is used to document ongoing infection.

Tick Copathogens

Ixodid ticks can be infected with multiple organisms [50]. Dual infections are reported in 4% to 30% of *B. burgdorferi* transmissions. This is an important consideration, because dual infections are associated with more severe Lyme disease [51,52]. Another tick-transmitted disorder may be misdiagnosed as Lyme disease. These infections often have distinct therapies [28, 51,53–59]. Within endemic areas in the Northeast, it has become increasingly common to screen for exposure to the agents of babesiosis and human granulocytic ehrlichiosis in anyone suspected of having Lyme disease.

Chronic Lyme Disease Syndrome

Treated Lyme disease patients, particularly those who are very symptomatic or who receive antibiotics during later infection, often note prolonged nonspecific symptoms such as fatigue, cognitive difficulties, headache, arthralgias, and myalgias [1,8,22,55,60,61]. Such patients are often considered to have chronic Lyme disease or post-Lyme disease syndrome. This syndrome has never been defined. Although some practitioners treat these patients with prolonged antibiotics for presumptive chronic *B. burgdorferi* infection, recent studies suggest most do not have an antibiotic responsive syndrome [22]. Potential explanations include an alternative diagnosis, infection with another tick pathogen, fixed damage, or sub-optimal initial therapy and ongoing *B. burgdorferi* infection. Persistent postinfectious symptoms may represent an immune or inflammatory process (similar to what is believed to be the case for chronic Lyme arthritis) occurring in a genetically susceptible host. Ongoing studies are attempting to clarify and define chronic Lyme disease syndrome. Such patients deserve a careful evaluation, and it should not be assumed that further antibiotics are required. There is a particular concern when duration of antibiotic use is driven by subjective symptom reports.

Conclusions

Lyme disease is a fascinating infection that has raised great public interest and controversy. It provides an interesting model to study how a pathogen causes neurologic disease. Current studies are focusing on improved diagnostic serology, a reliable assay for active infection, and more useful preventive vaccine strategies. The vast majority of symptomatically infected individuals do well with appropriate antibiotics. Ongoing studies are attempting to explain the paradigm of chronic Lyme disease syndrome, which may involve heterogeneous etiologies, as well as the pathogenesis of associated clinical disease syndromes. This should provide important information that can be generalized to other infectious disorders.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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