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Ticks, *Borrelia burgdorferi* and Lyme Disease

Keneler, *Borrelia burgdorferi* ve Lyme Hastalığı

Abstract

Lyme disease, which is caused by spirochete *Borrelia burgdorferi* sensu lato, is a tick-transmitted, multisystem infectious disease. It occurs in stages, with different clinical manifestations at each stage. Erythema migrans is the most frequent manifestation which occurs at the site of the tick bite. Borrelial lymphocytoma and acrodermatitis chronica atrophicans are late-stage cutaneous manifestations. Extracutaneous signs of infection most often involve the musculoskeletal, cardiovascular, and nervous systems. Serologic assays remain the mainstay of diagnosis. All stages of the disease are curable with appropriate antibiotic therapy.

Keywords: Lyme disease, *Borrelia burgdorferi*, erythema migrans, acrodermatitis chronica atrophicans, ticks, Ixodes

Öz

Lyme hastalığı *Borrelia burgdorferi* sensu lato grubu spiroketlerin sebep olduğu multisistemik bir enfeksiyon hastalığıdır. Her hastalık evresi değişik klinik bulgularla kendini gösterir. En sık klinik bulgusu kene ısırık yerinde gelişen eritema migranstır. Borrelial lenfositoma ve akrodermatitis kronika atrofikans geç dönemde gelişen deri bulgularıdır. Deri bulguları dışında kas-iskelet, kardiyovasküler ve sinir sistemi tutulumu da görülebilir. Tanı serolojik testler ile konulur. Hastalığın her evresi uygun antibiyotiklerle tedavi edilebilir.

Anahtar kelimeler: Lyme hastalığı, *Borrelia burgdorferi*, eritema migrans, akrodermatitis kronika atrofikans, keneler, Ixodes

Introduction

Lyme disease is a tick-transmitted multisystem infection, which is caused by the spirochetes of the *Borrelia burgdorferi* sensu lato. The disease derives its name from the town "Lyme" in Connecticut, America, where it was first recognised (1). Following the recognition of the disease and the discovery of the bacterial etiology (2,3), most of the cases were reported from North America, Scandinavia and central Europe. The most frequent manifestation of the disease, erythema migrans (EM), is an erythematous, edematous, gradually expanding annular rash at the site of the tick-bite. Recognition of this early lesion, together with other late-stage cutaneous manifestations of Lyme disease, is essential to start appropriate treatment and to prevent multisystem complications. Therefore, dermatologists have an important role in clinical diagnosis, since they are more familiar with both the typical and atypical cutaneous manifestations of the disease.

This review is intended to provide a current understanding of Lyme disease, with emphasis on its cutaneous manifestations.

Causative Organism

The genus *Borrelia* currently includes 13 closely related species known collectively as *Borrelia burgdorferi* sensu lato (4). However the most clinically relevant genospecies are *Borrelia burgdorferi* sensu stricto (*Borrelia burgdorferi*), *B. garinii* and *B. bafzelii*. *B. burgdorferi* is the sole cause of Lyme disease in North America, whereas all 3 genospecies are associated with the disease in Europe, leading to a wider variety of clinical manifestations in Europe than in North America (5-7).

Borrelia burgdorferi is a gram-negative, helical shaped spirochete. Structurally it is composed of inner and outer cell membranes, and 7-11 flagella located between these two membranes. The outer membrane contains various outer surface proteins (Osp) a through F, which

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are believed to play a role in adaptation and survival of the spirochete in vector and host organisms. Other antigenic structures of *Borrelia burgdorferi* are flagellin, which is the main component of flagella, and a 60-kDa 'common antigen', which is a member of the heat-shock protein family (8).

Epidemiology

Lyme disease occurs with similar frequencies in men and women and affects people of all ages (9). The incidence is relatively high in North America, central Europe (especially Germany, Austria, and Switzerland) and Scandinavia. Annual incidence in Germany was reported to be 20-35 cases per 100,000 people (10). The disease is transmitted to humans via the bite of the *Ixodes* tick. *I. scapularis* is the major vector in North America, whereas *I. ricinus* is the major vector in Europe (11,12). The tick has a 2-year, three stage life cycle (larval, nymphal, and adult), feeding only once during every cycle. It may become infected at any stage of its life by feeding on a host (small mammals, birds and reptiles), which is a natural reservoir for *Borrelia burgdorferi* (9). Humans can be an incidental host for the tick at any stage. During feeding, the spirochete in the gut of the tick migrates to its salivary gland, and transmission occurs through injection of the saliva (Figure 1). The risk of transmission of the disease is dependent on the duration of the stay in the specific tick endemic areas, and the duration of attachment of the infected ticks to the human body. The probability of transmission is low in the first 24 hours and more than 48 hours of attachment is needed for the transmission of the disease (13).

After transmission of *Borrelia burgdorferi* from the tick, the spirochete usually multiplies locally in the skin at the site of the tick bite, which elicits both innate and adaptive immunity. Later, *Borrelia burgdorferi* often disseminates through blood to other locations. Within several weeks to months, even without antibiotic treatment, widely disseminated infection is controlled by the immune mechanisms and clinically overt disease arises after only 0.3% to 1.4% of tick bites (14). However, without antibiotic therapy, spirochetes may survive for several more years, and may cause late-stage complications. The prevalence of specific infectious



Figure 1. A tick with its head embedded in the erythematous and edematous skin

complications reflects the distribution of genospecies in the region, with *Borrelia burgdorferi* more commonly associated with arthritis, *B. garinii* with neurologic disease and *B. afzelii* with skin manifestations (15).

Clinical Characteristics

Lyme disease generally occurs in stages, with different clinical manifestations at each stage. At the early stages the spirochete multiplies at the inoculation site (early localized infection), and disseminates to establish foci of infection elsewhere in the skin or other tissues (early disseminated infection). After months to years or following long periods of latent infection, it may cause a persistent disease (late infection) (16).

Cutaneous Manifestations of Lyme Disease

Skin manifestations of Lyme disease vary at different stages of the disease (Table 1). Most patients present at an early stage of infection, during the nymphal tick feeding period in late spring through early fall (17). The most common presenting sign is EM, which appears at the site of the tick bite, 1-2 weeks (up to 30 days) after the bite. It is recognized in ~90% of patients who have objective evidence of *Borrelia burgdorferi* infection (18,19). EM usually begins as an erythematous macule or papule that expands over time, occasionally developing a central clearing to form the annular-shaped bull's-eye lesion (Figure 2). Central vesiculation or necrosis may develop. Although any part on the human body can be affected, in children EM is localized more commonly on the head due to their small stature (20). EM is usually asymptomatic, but sometimes there is tingling, burning, pain, or mild pruritus. EM may be accompanied by constitutional signs and symptoms such as malaise, headache, fever, myalgia, or regional lymphadenopathy (21).

During early disseminated infection, multiple EM lesions may occur at sites distant from the site of tick attachment. Secondary lesions, which usually appear 3-5 weeks after the tick bite, are lighter, smaller, less edematous, and have less frequent central clearing compared with primary EM (22). During this period, some patients develop malar rash, diffuse erythema or rarely urticaria. Other common manifestations of early disseminated Lyme disease are cranial nerve palsies, especially facial nerve palsy, meningitis, and rarely carditis (8). Histopathologic picture of EM is characterized by a superficial and deep lymphocytic infiltrate containing plasma

Table 1. Cutaneous manifestations of Lyme disease

Localized infection	Disseminated infection	Late infection
Erythema migrans	Multiple erythema migrans	Acrodermatitis chronica atrophicans
	Malar rash	Localized fibrotic nodules
	Diffuse erythema or urticaria	
	Evanescient lesions	
	Lymphocytoma	

cells. Spirochetes may be demonstrated in the sections with Warthin-Starry stain (23).

Borrelial lymphocytoma is the rarest cutaneous manifestation of Lyme borreliosis, which has been reported almost exclusively from Europe. It is characterized by a painless, tumor-like nodule that typically appears on the ear lobe, nipple or scrotum, and usually lasts for months. *B. afzelii* is commonly isolated from the lesions. Histopathologic examination reveals spirochete by Warthin-Starry stain, as well as a dense dermal lymphocytic infiltrate, frequently with germinal centers (24).

Acrodermatitis chronica atrophicans (ACA) is the late stage cutaneous manifestation of Lyme disease. Similar to borrelial lymphocytoma, it is mostly caused by *B. afzelii* and mainly seen in Europe (25). It is characterized by chronic, progressive lesions, with inflammatory and atrophic stages. Although the lesions appear most commonly in the elderly, few cases of childhood ACA have also been reported (26). The disease occurs from 6 months to 8 years after the initial infection and can even be the presenting sign of the Lyme disease. Unilateral involvement of distal extremities is typical, particularly of extensor surfaces. The most commonly affected sites are the feet, legs, back of the hands and olecranon areas. More rarely, lesions on the face or trunk, or involvement in bilateral fashion have been reported (27). The disease course is characterized by an initially edematous inflammatory stage in which the epidermis remains intact while the dermis becomes swollen and inflamed. The skin is blue-red and the borders usually merge. In the later atrophic stage, as a result of chronic inflammation, collagen degeneration occurs with



Figure 2. Annular, bull's-eye shaped erythema migrans at the site of the tick bite

loss of elastic fibers and the skin resembles cigarette paper, with loss of hair and prominence of blood vessels (Figure 3a, 3b). Rarely subcutaneous fibrotic nodules may occur adjacent to joints (Figure 4).

The clinical evolution from the early inflammatory edematous stage to the atrophic stage of ACA reflects on histological findings. In the early inflammatory phase telangiectasiae, dermal edema and perivascular lymphoplasmacytic infiltrate are observed, whereas epidermal atrophy, destruction of epidermal appendages and sclerosis become prominent in



Figure 3. a) Blue-red discoloration of bilateral ankles and edematous appearance of the right medial malleolus at the early stage of acrodermatitis chronica atrophicans, b) Skin atrophy of bilateral dorsal hands, with cigarette paper-like appearance and prominence of blood vessels at the late stage of the disease



Figure 4. Periarticular fibrotic nodules on the elbow, which is a rare late stage manifestation of Lyme disease

the later stages. Once established, the atrophy usually persists despite treatment (28). Peripheral neuropathy of the involved limb occurs in more than half of patients with a long-lasting ACA lesion (29).

Extracutaneous Manifestations of Lyme Disease

Musculoskeletal symptoms can occur at all stages of infection. Migratory musculoskeletal pain accompanied by fever, headache and fatigue is common early after infection; however frank arthritis mostly occurs at the late stage of the disease. Months after the onset of the illness 60% of patients develop a monoarticular or oligoarticular arthritis, which affects the large joints, especially the knees (30). The joint becomes swollen and tender lasting hours to days, but intense pain associated with septic arthritis is usually not present (9). Although antibiotic treatment is highly effective for arthritis, a small percentage of patients develop persistent joint inflammation despite one or two courses of oral or intravenous antibiotics. This disorder, which is defined as antibiotic-refractory Lyme arthritis, may be associated with an autoimmune mechanism (31).

Neurologic manifestations may appear weeks to a few months after a tick bite, including cranial neuritis, sensory and motor radiculoneuropathies, paresthesias, meningitis or encephalomyelitis. The usual pattern consists of fluctuating symptoms of meningitis with cranial (seventh cranial nerve palsy) or peripheral radiculoneuropathy (32). After long periods of latent infection, 10% of patients may develop chronic neuroborreliosis (33). Neurologic symptoms are seen more frequently in Europe, due to the neurotropism of *B. burgdorferi*, which is isolated mainly in Europe (34).

Lyme carditis may appear as shortness of breath, palpitations, dizziness and anxiety that result from varying degrees

of atrioventricular nodal block; other manifestations of myopericarditis occur less frequently. Lyme carditis can progress to complete heart block and cause sudden death (35). In Europe, *Borrelia burgdorferi* has been isolated from endomyocardial biopsy samples from several patients with chronic dilated cardiomyopathy (36,37).

Diagnosis

Positive culture of *Borrelia burgdorferi* from patient specimens in Barbour-Stoenner-Kelly medium permits definitive diagnosis. In the early stages of the infection *Borrelia burgdorferi* can be cultured from EM lesions, less often from blood samples, and rarely from cerebrospinal fluid. Later in the infection, PCR testing is superior to culture in the detection of *Borrelia burgdorferi* from the joint fluid (38). However PCR may yield positive results even after antibiotic treatment, since DNA from the organism may persist for some time after the bacteria are no longer viable (39).

Serologic assays remain the mainstay of diagnostic testing for Lyme disease. The recommended approach is using an enzyme-linked immunosorbent assay (ELISA) followed by Western blotting if the ELISA result is positive or equivocal (40). The two-tier assay has low sensitivity in early infection, but it is highly sensitive after 6-8 weeks of untreated infection. A positive serological test does not mean that a patient necessarily has active Lyme disease. Therefore, additional testing, such as tests for intrathecal antibody production in patients with suspected Lyme neuroborreliosis, polymerase chain reaction (PCR) of joint fluid for suspected Lyme arthritis, or skin biopsies for suspected ACA or borrelial lymphocytoma, might increase the diagnostic accuracy (7). After antibiotic treatment, antibody titers decline slowly, but IgG and even IgM responses may persist for many years (41).

Table 2. Recommended treatment for Lyme disease

Manifestation	Treatment	Duration
Early disease - Adults	Doxycyclin 100 mg orally twice a day	14-21 days
	Amoxicillin 500 mg orally three times a day In case of ceftriaxone or penicillin allergy: Cefuroxime axetil 500 mg orally twice a day	14-21 days
- Children <8 years	Amoxicillin 250 mg orally, three times a day or 50 mg/kg/day in 3 divided doses	14-21 days
	In case of ceftriaxone or penicillin allergy: Cefuroxime axetil 30 mg/kg/day in 2 divided doses	14-21 days
Arthritis (intermittent or chronic)	Doxycyclin 100 mg orally twice a day	30-60 days
	Amoxicillin 500 mg orally three times a day	30-60 days
	Ceftriaxone 2 g IV once a day	14-28 days
	Penicillin G 20 million U IV daily in four divided doses	14-28 days
Neurologic disease (early or late)	Ceftriaxone 2 g IV once a day	14-28 days
	Penicillin G 20 million U IV daily in four divided doses	14-28 days
	In case of ceftriaxone or penicillin allergy: Doxycyclin 100 mg orally three times a day	14-28 days
- Facial palsy alone	Oral regimens are adequate	14-21 days
Cardiac disease - First-degree arterioventricular block	Oral regimens are adequate	14-21 days
	- High-degree arterioventricular block	Ceftriaxone 2 g IV once a day Penicillin G 20 million U IV daily in four divided doses

Thus, serologic tests are not indicated in routine follow up, they only assess exposure history. False-positive results occur when first-tier ELISA is omitted, when non-evidence-based criteria are used to interpret immunoblot findings and when nonspecific weak bands are reported as positive.

An alternative first-tier test is C6 peptide enzyme-linked immunosorbent assay (ELISA), which is based on an invariant region of the VlsE protein (42). The principal advantage of the C6 peptide ELISA is the early IgG response, and therefore an IgM test is not necessary. Application of this method as a stand-alone test or in the second tier of a two-tiered algorithm may provide better sensitivity and specificity compared to the conventional two-tiered sonicate ELISA and Western blot assays (43,44).

Treatment

Oral antibiotics (doxycycline, amoxicillin or cefuroxime axetil) are first-line therapies for early localized or disseminated infection. It was shown that doxycycline, amoxicillin, and cefuroxime axetil had similar therapeutic results in the early stages of the disease (45,46). Erythromycin and azithromycin are less effective than other oral antibiotics, which can be used as second-line treatment. Borrelial burgdorferi is resistant to specific fluoroquinolones, rifampicin, and first-generation cephalosporins (47,48). The recommended course of treatment is 14-21 days. Two to 4 weeks of intravenous therapy with ceftriaxone is the treatment of choice for patients with objective neurologic abnormalities, severe carditis or arthritis that does not improve with oral antibiotics. Alternative parenteral antibiotics are cefotaxime and intravenous penicillin. Standard therapy for the stage and manifestation of the illness may be sufficient for pregnant patients, except that doxycycline should be avoided (Table 2) (48). In general, earlier manifestations of illness respond more rapidly to antibiotic treatment than later ones such as arthritis. Within 24 h of the start of the antibiotics, 15% of patients may transiently have intensified signs and symptoms consistent with a Jarisch-Herxheimer reaction, which should be treated symptomatically (9).

Posttreatment Lyme disease syndrome refers to fatigue, cognitive problems or musculoskeletal pain that last for >6 months after a documented episode of Lyme disease. The frequency with which posttreatment Lyme disease syndrome occurs is believed to be below 10% (17). This post-infectious syndrome occurs more frequently in patients whose symptoms are suggestive of early dissemination of the spirochete to the nervous system, particularly when treatment is delayed. Such patients are best treated symptomatically rather than with prolonged courses of antibiotic therapy (49).

Prevention

Preventive measures against infection include protective clothing, use of tick repellents on skin and clothing, careful inspection of the skin (including scalp) for the ticks and if found, removing the tick rapidly. Tweezers are suitable instruments for removing them. Any superfluous manipulation of ticks, e.g., crushing them or covering them with oils or ointments, should be avoided, as these maneuvers may promote the regurgitation of blood and thereby increase the likelihood of borrelial transmission. If some of the mouth parts remain

embedded in the skin they should be left behind because they are eventually extruded. Once the tick has been removed, the puncture site should be meticulously disinfected.

Specific treatment is not necessary after the removal of a recognized tick. However, a single 200 mg dose of doxycycline effectively prevents Lyme borreliosis when given within 72 h after the tick bite occurs (50).

A commercial Lyme disease vaccine consisting of recombinant OspA with adjuvant had been developed. However, it was withdrawn from the market due to poor public acceptance and the complaints of post-vaccination fatigue (9). Currently, there is no vaccine available to prevent Lyme disease. Thus, precautions to prevent tick bites should be taken to prevent new infections.

Abbreviations

ACA	Acrodermatitis chronica atrophicans
EM	Erythema migrans
ELISA	Enzyme-linked immunosorbent assay
Osp	Outer surface proteins

Authorship Contributions

Concept: Işın Sinem Bağcı, Thomas Ruzicka, Design: Işın Sinem Bağcı, Thomas Ruzicka, Data Collection or Processing: Işın Sinem Bağcı, Analysis or Interpretation: Işın Sinem Bağcı, Thomas Ruzicka, Literature Search: Işın Sinem Bağcı, Writing: Işın Sinem Bağcı.

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