Lyme Borreliosis

55

Jana Hercogová

Key Points

- Lyme borreliosis is an inflammatory disease caused by the spirochaete *Borrelia burgdorferi* which is transmitted by tick (mainly of the genus *Ixodes*).
- It is an anthropozoonosis which manifests itself as a multisystem disorder of the skin and other organs (joints, nerves, heart, eye, etc.).
- Cutaneous manifestations of Lyme borreliosis include erythema migrans, borrelial lymphocytoma and acrodermatitis chronica atrophicans.
- The diagnosis of Lyme borreliosis is based on the history of tick exposure, the characteristic clinical picture and confirmation of *B. burgdorferi* infection by serological tests.
- Antibiotic therapy should be started as soon as possible after the diagnosis has been made. Borreliae are sensitive to four groups of antibiotics—penicillins, cephalosporins (third generation and cefuroxime axetil), tetracyclines and macrolides. The drugs of choice for oral treatment of Lyme borreliosis are doxycycline and amoxicillin and for parenteral treatment ceftriaxone, cefotaxime and penicillin G.

J. Hercogová (✉)
Dermatovenereology Department, 2nd Medical Faculty, Charles University, Institute of Clinical and Experimental Medicine, Bulovka Hospital, Prague, Czech Republic

Definition and Epidemiology

Lyme borreliosis is an inflammatory disease caused by the spirochaete *Borrelia burgdorferi* which is transmitted by tick (mainly of the genus *Ixodes*). It is an anthropozoonosis which manifests itself as a multisystem disorder of the skin and other organs (joints, nerves, heart, eye, etc.).

Lyme borreliosis is the most common vector-borne disease in Europe and the USA. Ticks of the genus *Ixodes* are the vectors that transmit the infection to mammals in endemic areas—in the North American and Euro-Asian continents. In Europe, Austria, Slovenia, Sweden and the Czech Republic belong to the most endemic areas (incidence could raises to 100 cases per 100,000 inhabitants). *B. burgdorferi* has been isolated from patients worldwide. Cutaneous involvement is the most frequent manifestation of the disease: it represents 60–80% of all reported cases. Concerning cutaneous symptoms, erythema migrans is the most prevalent (approximately 85%), followed by acrodermatitis chronica atrophicans (10%) and borrelial lymphocytoma (5%). Concrete cutaneous manifestations affect different age groups—erythema migrans is mainly present in middle-aged adults (30–50 years), borrelial lymphocytoma is typical for children and acrodermatitis is a disease of the elderly.

A. D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
https://doi.org/10.1007/978-3-031-15130-9_55

Basic Concepts of Pathogenesis

The aetiological agent, *B. burgdorferi* sensu lato, has been subdivided into three genospecies causing the human disease: *B. burgdorferi* sensu stricto, *B. afzelii* and *B. garinii*. Strains of all three species have been isolated from patients in Europe, whereas only the first species is involved in the USA. Some studies show that *B. afzelii* represents a dominant human skin isolate in Europe. Antigenic differences of three genospecies may explain the variability of clinical manifestations in patients with Lyme borreliosis. Genetic analysis of *B. garinii* OspA serotype 4 strains is correlated with the development of neuroborreliosis. *B. afzelii* OspA serotype 2 closely correlates with the development of acrodermatitis chronica atrophicans.

After the tick bite, borreliae spread in the dermis causing cutaneous symptom of the early localized stage (erythema migrans and borrelial lymphocytoma). Antibody immune response could be demonstrated in 3–4 weeks in the IgM class and in 4–6 weeks in the IgG class. Haematogenic spread of borreliae follows weeks to months after the tick bite and can manifest itself as the early disseminated stage of the disease. The development of the chronic stage is a subject of ongoing studies. The question is whether the symptoms are a result of the host immune response against organism or even against tissue autoantigens. T-cell-mediated immunity might be responsible for inducing and exacerbating cardiac and joint symptoms. T-cell-mediated immunopathology may result from the antigenic specificity of T cell, the activation of a specific T-cell subset or ability of persisting antibodies to induce hypersensitive auto-reactive T cells in the joints and the heart. Auto-reactive B-lymphocytes as well as significantly raised concentrations of IgA rheumatoid factor were proven in the serum of patients with the chronic stage of Lyme borreliosis; production of these antibodies may be a result of B-cell auto-reactivity.

Clinical Presentation

Cutaneous manifestations of Lyme borreliosis include erythema migrans, borrelial lymphocytoma and acrodermatitis chronic atrophicans; morphoea and its initial stage, lichen sclerosus et atrophicus, are considered to be polyaetiological entities in which borreliae (*B. afzelii* and *B. garinii*) were isolated from morphoea lesions. Extracutaneous manifestations are variable (Table 55.1).

Erythema migrans is an early localized form of Lyme borreliosis. It appears 3–30 days after the tick bite and is defined as a red patch, bigger than 4 cm in diameter at the site of the tick bite which spreads centrifugally and can reach several decimetres in diameter. Three main clinical types are known: (a) homogenous (a red, sharply demarcated patch without a central clearing), (b) annular (a red, sharply demarcated patch with a central clearing), and (c) iris-like (concentric annular patches). From time to time, also multiple or bullous types could be present. A central reddish macule, representing the site of the tick bite, may be apparent in any of these three clinical types.

Erythema migrans can be present anywhere on the body surface, but the lower extremities are

Table 55.1 Clinical manifestations of Lyme borreliosis

Early stage
Localized infection
Erythema migrans (annular, macular and concentric)
Borrelial lymphocytoma (papular and infiltrative)
Disseminated infection
Multiple erythemata migrantia
“Flu-like” symptoms
Meningitis, manigoradiculoneuritis
Endocarditis, myocarditis, pericarditis
Arthritis, tenosynovitis
Hepatitis, keratitis and conjunctivitis
Chronic stage
Acrodermatitis chronica atrophicans (macular, telangiectatic, fibrotic and atrophic)
Chronic encephalitis, encephalomyelitis, polyneuritis
Chronic arthritis

the most frequent sites. In children, the head and neck are also usually affected.

Borrelial lymphocytoma is a bluish-red papule, nodule or plaque, 1–3 cm in diameter, localized on the ear lobe. The areola mammae, scrotum and nose are other typical sites.

Acrodermatitis chronica atrophicans starts as an inflammatory stage which evolves into an atrophic stage. Firstly, bluish-red, not sharply demarcated patch(es) or plaque(s) appear on the dorsal aspect of the foot or hand. Predilection sites include the skin above the bony prominences (on the lower extremities, the ankle, lateral aspects of the foot, fingers and knee and on the upper extremities, fingers and elbow). Lesions usually spread from distal to proximal sites, including the trunk and face. Four clinical types of the lesions can be differentiated: (a) erythematous lesions (bluish-red patches and plaques in cases of swelling), (b) telangiectatic lesions (telangiectasias predominately, red patches), (c) fibrous lesions (firm, bluish-red of skin-coloured nodules, mainly above the elbow, ulna or small joints of the hand) and (d) atrophic lesions (thin skin with wrinkles and prominent vessels).

Diagnosis

The diagnosis of Lyme borreliosis is based on the history of tick exposure, the characteristic clinical picture and confirmation of *B. burgdorferi* infection by serological tests (with the exception of early pathognomonic cutaneous manifestations of the disease, e.g. annular erythema migrans and borrelial lymphocytoma which is localized on the ear lobe and is present in children). Histopathological examination should be performed in acrodermatitis chronic atrophicans patients and in those where the diagnosis is not clear from a clinical point of view.

Direct proof of borrelial infection includes isolation (allowing the demonstration of live *B. burgdorferi*, e.g. in the skin, synovial fluid, myocardium) and histopathological detection of the microorganisms in the tissue by a modified Dieterle's stain or a modified Steiner's method, electron microscopy, DNA hybridization and polymerase chain reaction (nested PCR and quantitative PCR). PCR testing of cutaneous lesions is helpful to confirm the diagnosis in clinically atypical cases.

Indirect methods include enzyme-linked immunosorbent assay (ELISA) and immunoblotting. Two-step serological testing is recommended in which a serum specimen with a positive test result by the ELISA is further tested with immunoblotting. The standardization of an immunoblotting method for the diagnosis of Lyme borreliosis would require agreement on the strains used for antigen preparation. This approach would not be possible in Europe due to different local prevalences of genospecies of *B. burgdorferi* sensu lato and also to heterogeneity within those strains. To date, none of the serological tests should be termed as a "screening" test. Special attention should be given to patients in whom serological tests could be false positive (other spirochetal infections, autoimmune disorders) and/or false negative (immunocompromised patients).

Histopathological examination of the erythema migrans lesion shows superficial perivascular dermatitis, composed of lymphocytic infiltrate with plasma cells and eosinophils. Borrelial lymphocytoma is a pseudolymphoma; lymphocytes are top heavy, without nuclear atypia, and plasma cells can be present. Acrodermatitis chronica atrophicans shows superficial perivascular or lichenoid dermatitis, lymphocytic infiltrate with plasma cells, epidermal atrophy, dilated vessels in the upper part of the dermis and orthohyperkeratosis. Later on, degeneration of elastic and collagen fibres, as well as gland adnexae, could follow.

Differential Diagnosis

Erythema migrans should be differentiated from erysipelas, superficial tinea, fixed drug eruption, discoid cutaneous lupus erythematodes, granuloma annulare, morphoea and contact dermatitis.

Borrelial lymphocytoma could be similar to histiocytoma, keloid, angioma, Kaposi's sarcoma, granuloma faciale, granuloma annulare,

sarcoidosis and lupus erythematodes. In all cases, histopathological examination is helpful. Malignant lymphoma can be distinguished by immunohistochemical examination.

Acrodermatitis chronica atrophicans can mimic circulatory insufficiency, perniones, morphoea and dermatomyositis; fibrotic papules and nodules are considered to be rheumatic nodules or gouty tophi.

General Principles of Treatment

Antibiotic therapy should be started as soon as possible after the diagnosis has been made. Some studies demonstrate that even an appropriate antibiotic regimen may not always eradicate the spirochete. On the one hand, the treatment of disseminated Lyme borreliosis for 3 months may not be sufficient: the spirochetes can remain in serum, skin and other tissues, and clinical relapses can occur. However, it remains unresolved whether the prognosis of patients with disseminated Lyme borreliosis could be improved by longer initial treatment. On the other hand, the outcomes of most persons diagnosed as having Lyme borreliosis who are treated with antimicrobial agents are excellent. Extracutaneous manifestations of Lyme borreliosis are described after any antibiotic regimen in up to 10% patients. Recently, treatment trials for post-Lyme disease symptoms were revised, and authors did not find any data supporting the benefit of retreatment of the patients who had been treated with antibiotics previously.

Cutaneous manifestations disappear after the therapy, but immediate disappearance of borrelial lymphocytoma and acrodermatitis chronica atrophicans during antibiotic therapy is exceptional. Those lesions begin to fade and lose the swelling, but resolution can take up to 6 months. The degenerative changes in acrodermatitis are not reversible. No significant differences were found in the outcome of erythema migrans after 1 year in patients whose immune system was impaired compared to previously healthy individuals.

The immunological response after antibiotic therapy appears to be abrogated, so levels of antiborrelial antibodies cannot be used as proof of successful therapy. Furthermore, the antibody titre development after therapy is unpredictable and variable, and it is largely uncorrelated with the clinical course. It was also shown that even after the proper antibiotic therapy, *B. burgdorferi* DNA could persist up to 6 months.

Recommended Therapies

Borreliae are sensitive to four groups of antibiotics—penicillins, cephalosporins (third generation and cefuroxime axetil), tetracyclines and macrolides. The drugs of choice for oral treatment of Lyme borreliosis are doxycycline and amoxicillin and for parenteral treatment ceftriaxone, cefotaxime and penicillin G. Ceftriaxone is primarily used as a treatment for patients with extracutaneous (joint, neurological, cardiac) and multiple cutaneous manifestations. If the coinfection with ehrlichiosis is suspected, doxycycline is the drug of choice. Doxycycline is also preferred in cases of penicillin-cephalosporin allergy since erythromycin has inferior efficacy. Children with solitary erythema migrans could be treated with phenoxymethyl penicillin and cefuroxime axetil; however, drug-related side effects were more frequently observed with cefuroxime axetil. Minocycline causes teeth discoloration even in young adults and discoloration of the skin, nails, sclera and conjunctivae. Vertigo, ataxia and dizziness have been described during minocycline therapy. These symptoms are a major disadvantage, in particular for patients with neurological symptoms, as in Lyme disease.

Recommended therapies for uncomplicated erythema migrans include oral doxycycline 200 mg daily (divided into two doses every 12 h) or amoxicillin 3 g daily (divided into three doses every 8 h) for 15 days. If any general signs or symptoms (subfebrilia, malaise, fatigue, arthralgias, myalgias, meningism, conjunctivitis, etc.) are present even if for 1 day, the duration of antibiotic therapy should be 20 days. In case of penicillin of tetracycline allergy, azithromycin is prescribed (500 mg daily p.o. for 10 days and for

15 days in the presence of general signs or symptoms).

Borrelial lymphocytoma is treated with the same antibiotic regimen; only the duration of therapy is at minimum 20 days. Acrodermatitis chronica atrophicans patients are given the same oral antibiotics for 25–30 days, but in the presence of any extracutaneous manifestations, parenteral therapy is needed—ceftriaxone 2 g i.v. daily in one dose of penicillin G i.v. 20 million units daily (divided into 4 doses of 5 million units every 6 h) for 15 days followed by oral antibiotic (as in the early stage) for the next 15 days.

Special attention should be given to pregnant women with Lyme borreliosis. Penicillins, macrolides and ceftriaxone are used, but antibiotic administration depends on the time of tick bite; if the tick bite is suspected during the trimester, then parenteral antibiotics are used. On the other hand, if the tick bite occurs later in pregnancy and the patient has no extracutaneous symptoms or signs, oral antibiotics are sufficient for therapy.

Prevention

Prevention of Lyme borreliosis includes avoiding exposure to tick bites by limiting outdoor activities in endemic areas, using tick repellents containing diethyltoluamide (DEET) 10–35% or picaridin 20%, tucking in clothing and frequent skin inspection for early detection and correct removal of ticks. Persons who have undergone tick removal should be monitored up to 30 days for signs and symptoms.

Antibiotic prophylaxis has not been shown to be effective in reducing the risk of acquiring Lyme borreliosis. Some authors recommend local antibiotics after the tick bite; the other did not confirm the efficacy of topical antibiotics in preventing dissemination of the disease.

Vaccination trials showed that a single recombinant outer surface protein A (OspA) appears to be safe and immunogenic in man. A single antigen OspA vaccine in not effective in Eurasia, where more heterogeneous species of borrelia and more variable OspA are present. In Eurasia, compared to the USA, a vaccine must be effective against all subgroups of the borrelia spirochaete. Some protective immunity against borrelia infection in laboratory animals was demonstrated by some other *B. burgdorferi* proteins, for example OspB and OspC.

Recently, it was shown by the study from Northeastern US patients that those treated for early Lyme disease develop protective immunity that is strain specific and lasts for at least 6 years. Repeated serologic testing is of very limited value for assessing therapy efficacy and therefore not recommended in the follow-up of dermatoborrelioses patients.

Further Reading

Aberer E, Keldorfer M, Binder B, Shauperl H. The outcome of Lyme borreliosis in children. Wien Klin Wochenschr. 1999;111(22–23):941–4.

Arnez M, Radsel-Medvescek A, Pieterski-Rigler D, et al. Comparison of cefuroxime axetil and phenoxymethyl penicillin for the treatment of children with solitary erythema migrans. Wien Klin Wochenschr. 1999;111(22–23):916–22.

Biesiada G, Czepiel J, Leśniak MR, Garlicki A, Mach T. Lyme disease review. Arch Med Sci. 2012;8(6):978–82.

Cunha BA. Minocycline versus doxycycline in the treatment of Lyme neuroborreliosis. Clin Infect Dis. 2000;30(1):237–8.

Dotevall I, Hagberg I. Adverse effects of minocycline versus doxycycline in the treatment of Lyme neuroborreliosis. Clin Infect Dis. 2000;30(1):410–1.

Eriksson P, Schröder MT, Niiranen K, Nevanlinna A, Panelius J, Ranki A. The many faces of solitary and multiple erythema migrans. Acta Derm Venereol. 2013;93(6):693–700.

Gilmore RD Jr, Mbow ML. Conformational nature of the Borrelia burgdorferi B31 outer surface protein C protective epitope. Infect Immun. 1999;67(10):5463–9.

Hayney MS, Grunske MM, Boh LE. Lyme disease prevention and vaccine prophylaxis. Ann Pharmacother. 1999;33:723–9.

Hercogova J, Brzonova I. Lyme disease in central Europe. Curr Opin Infect Dis. 2001;14:133.

Hercogová J, Vaňousová D. Syphilis and borreliosis during pregnancy. Dermatol Ther. 2008;21(3):205–9.

Khatchikian CE, Nadelman RB, Nowakowski J, Schwartz I, Wormser GP, Brisson D. Evidence for strain-specific immunity in patients treated for early Lyme disease. Infect Immun. 2014;82:1408–13.

Klempner MS, Baker PJ, Shapiro ED, Marques A, Dattwyler RJ, Halperin JJ, Wormser GP. Treatment

trials for post-Lyme disease symptoms revisited. Am J Med. 2013;126(8):665–9.
Maraspin V, Lotric-Furlan S, Cimperman J, et al. Erythema migrans in the immunocompromised host. Wien Klin Wochenschr. 1999;111(22–23):923–32.
Moniuszko A, Pancewicz S, Czupryna P, Dunaj J, Guziejko K, Zajkowska J. Erythema migrans as a patognomic symptom of Lyme disease [Article in Polish]. Pol Merkur Lekarski. 2013;35(208):230–2.
Mullegger RR, Glatz M. Is serological follow-up useful for patients with cutaneous Lyme borreliosis? Curr Probl Dermatol. 2009;37:178–82.
Oksi J, Marjamaki M, Nikoskelainen J, Viljanen MK. Borrelia burgdorferi detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. Ann Med. 1999;31(3):225–32.
Pícha D, Moravcová L, Vaňousová D, Hercoogvá J, Blechová Z. DNA persistence after treatment of Lyme borreliosis. Folia Microbiol (Praha). 2014;59:115–25.
Roupakias S, Mitsakou P, Nimer AA. Tick removal. J Prev Med Hyg. 2011;52(1):40–4.
Seltyer EG, Gerber MA, Cartter ML, et al. Long-term outcomes of persons with Lyme disease. JAMA. 2000;283(5):609–16.
Shadick NA, Phillips CB, Sangha O, et al. Musculoskeletal and neurologic outcomes in patients with previously treated Lyme disease. Ann Intern Med. 1999;131(12):919–26.
Stanek G, Breier F, Menyinger G, et al. Erythema migrans and serodiagnosis by enzyme immunoassay and immunoblot with three Borrelia species. Wien Klin Wochenschr. 1999;111(22–23):951–6.
Wahlberg P. Vaccination against Lyme borreliosis. Ann Med. 1999;31:233–5.
Warshafsky S, Nowakowski J, Nadelman RB, et al. Efficacy of antibiotic prophylaxis for prevention of Lyme disease. J Gen Intern Med. 1996;11:329–33.
Wormser GP, Daniels TJ, Bittker S, Cooper D, Wang G, Pavia CS. Failure of topical antibiotics to prevent disseminated Borrelia burgdorferi infection following a tick bite in C3H/HeJ mice. J Infect Dis. 2012;205(6):991–4.