Lyme disease: review

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Abstract

Lyme disease is a multi-organ animal-borne disease, caused by spirochetes of *Borrelia burgdorferi* (Bb), which typically affect the skin, nervous system, musculoskeletal system and heart. A history of confirmed exposure to tick bites, typical signs and symptoms of Lyme borreliosis and positive tests for anti-Bb antibodies, are the basis of a diagnosis. A two-step diagnosis is necessary: the first step is based on a high sensitivity ELISA test with positive results confirmed by a more specific Western blot assay. Antibiotic therapy is curative in most cases, but some patients develop chronic symptoms, which do not respond to antibiotics. The aim of this review is to summarize our current knowledge of the symptoms, clinical diagnosis and treatment of Lyme borreliosis.

Key words: Lyme borreliosis, tick, borreliosis.

Introduction

Lyme borreliosis, also known as Lyme disease, is a multi-organ animal-borne disease, caused by bacteria – spirochetes of the *Borrelia* species classified as *Borrelia burgdorferi* (Bb) strain (*sensu lato*). It is the most common tick-borne infectious disease in Europe. The infection is transmitted by ticks of the species *Ixodes ricinus*. Spirochetes have also been isolated from mosquitoes, fleas and flies, but they were found to play no role in the transmission of the infection to humans. In Europe, *I. ricinus* ticks usually prey on rodents and deer, which are the key Bb reservoir [1-4].

At least 11 Bb genostrains are known, but not all of them are considered pathogenic. In Europe Lyme borreliosis is caused by *B. garinii*, which is more likely to cause neuroborreliosis, with *B. afzelii* causing atrophic chronic acrodermatitis (ACA), and Bb itself (*Borrelia burgdorferi sensu stricto*). Most recent reports suggest that in Europe, pathogenic strains also include *B. lusitaniae*, *B. valaisiana* and *B. spielmani* [5-7].

Humans are infected through a tick bite to the skin. Bb has to be attached for at least 24 h for an infection to result. The risk of infection increases with length of time of human exposure to the tick, approaching 100% on the third day. Thus, early removal of ticks is the best method of Lyme borreliosis prophylaxis [2].

The term Lyme borreliosis points directly to the etiology of the disease, but the term Lyme disease is also used in the literature.

Epidemiology

The percentage of the population testing positive for anti-Bb antibodies varies in different European countries (approximately 5-25%). Some of these patients have no symptoms of Lyme disease. Lyme borreliosis is most prevalent in Central and Eastern Europe. In Austria and Slovenia it reaches 120-130 cases per 100 000 inhabitants. In Poland approximately seven thousand new cases were reported in 2007 [6, 8-11].

In humans the signs and symptoms of Lyme borreliosis most frequently appear in spring, summer and early autumn. This is due to the life cycle of ticks, which feed on blood only once in each of three stages (larva, nymph and adult tick). Larvae emerge from eggs laid in spring, attach to small vertebrates, who are their first hosts, and become infected with spirochetes when attached to an infected host. Larvae molt into nymphs, and during the subsequent spring and summer, from mid-May to late July, the nymphs feed for the second time. Tick nymphs before the meal are only the size of a poppy seed and thus difficult to notice, but are very active in transmitting a Bb infection which can cause numerous infections in humans. In late summer the nymphs transform into adult forms (the size of an apple seed) and in autumn or even in winter, adults feed on a third host and reproduce; then the life cycle repeats [4, 7].

Clinical picture

According to the European definition adopted at the WHO conference in Serock in 1995, Lyme borreliosis is diagnosed in a patient who has been previously exposed to ticks and who subsequently developed the typical signs and symptoms associated with Lyme borreliosis, affecting the skin, nervous system, musculoskeletal system and heart [2, 7].

The Asbrink and Hovmark classification defines two stages of the disease – early and late Lyme borreliosis [8]. Approximately half of the patients with the early disease develop a circumscribed skin lesion – erythema migrans (EM). This lesion is pathognomonic for Lyme borreliosis. The EM usually appears within 3 to 30 days after the tick bite, not later than in 3 months, most frequently on the lower extremities (approximately 54%) and trunk (approximately 29%). The lesion gradually extends, developing a central clearing and reaching over 5 cm in diameter. Sometimes atypical erythemas without a central clearing or with vesicles are observed. Unfortunately, this important sign, allowing for a diagnosis of Lyme borreliosis without subsequent diagnostic studies, is absent in some patients. Another – very rare – skin lesion is borrelial lymphocytoma, a bluish-red nodule appearing usually on the ear lobe or nipple within months or years of an infection. What is of particular importance is that antibiotic therapy instituted in this phase of the disease is effective in almost 99% of patients. In cases where a patient has not been treated in the phase of EM, the treatment was markedly delayed or when EM has been absent, the disease may progress to the disseminated stage and affect other organs. Also, multiple EM may develop, in which skin lesions are smaller and their number varies from two to several dozen [10-13].

Musculoskeletal system involvement is typical for the disease. This form develops within several weeks up to years after the tick bite, but usually after 6 months. In the first few weeks from the beginning of infection in approximately 60 % of patients it is limited to migrant muscle, large joint and bone pain. Some patients report recurrent pain in their bones, joints or periarticular soft tissues. These problems are usually unilateral and may either spontaneously subside or develop into full-blown arthritis [14]. A typical feature is arthritis with effusion, affecting a large joint (very often a knee joint). It is usually asymmetrical and is accompanied by joint edema without erythema, generally with several weeks of remissions and relapses which can cause joint dysfunction [7, 11, 15].

Central nervous system (CNS) involvement may develop even when EM is still present, and neurological signs and symptoms are highly variable. Typically, neurological signs and symptoms appear from between approximately months to years after infection. In Europe 70% of patients with CNS involvement develop Bannwarth syndrome, including lymphocytic meningitis, cranial nerve palsies, primarily affecting nerve VII (or VI, V, III and VIII) and radicular pains. Meningitis is initially limited to the base of the brain and is associated with moderate headaches; typical signs of meningitis are less frequent and the temperature is usually stable. Radicular pains result from direct spirochete invasion of nerve roots; the pain usually increases during nighttime and is resolved after antibiotic therapy, but not after analgesics. Radicular pain may be the only symptom of Bannwarth syndrome. Within several days or weeks, untreated patients with such a course of Lyme borreliosis can develop flaccid palsies and sensory abnormalities. A less frequent form of neuroborreliosis is encephalitis and/or myelitis. Chronic encephalomyelitis has an irregular course, mimicking cerebral ischemic attacks. It is manifested by limb paresis, speech abnormalities, cerebellar signs, disturbances of visual fields, seizures, lethargy and progressive dementia. In Europe neuroborreliosis, both isolated and combined with joint symptoms, is more frequent than in the USA. This is due to geographical differences in prevalence of the *Borrelia garinii* genostrain [7, 16-20].

The heart is involved within several weeks of the infection in approximately 4-8% of infected patients. The heart disease displays a form of conduction abnormalities, particularly atrioventricular blocks of various grades, which are resolved spontaneously in 95% of patients. Cases of carditis, exudative pericarditis and (very rarely) pancarditis have also been described [19, 21, 22].

When neurological, rheumatic or other organ lesions persist chronicly, the second stage – chronic (late) Lyme borreliosis – is diagnosed [2].

Atrophic chronic acrodermatitis (ACA) is a particular form of late Lyme borreliosis developing in patients infected with *B. afzelii*. The ACA manifests many years after the infection, usually in elderly persons. It is also classified as late Lyme borreliosis. The lesions are located on lower extremities and progress slowly. ACA may develop despite a lack of any earlier signs and symptoms of Lyme borreliosis. In approximately 20% of patients it is located on the same extremity where EM has previously been present. The initial inflammatory phase is characterized by a bluish-red discoloration of skin with focal hyperpigmentation and edema, usually located on distal parts of extremities. Patients may complain of pain, pruritus or paresthesias of the affected skin. Untreated ACA progresses to the atrophic phase, which is characterized by epidermal thinning with visible dilated veins. Moreover, peripheral neuropathy and degenerative and inflammatory changes of adjacent joints may develop. Diagnosis may be difficult and is based on a clinical picture combined with positive serological testing for Bb and histological examination. Histology reveals lymphocytic infiltrates with dominant T cells (CD3 and CD4) and some plasma cells. The atrophic phase is also associated with collagen degeneration [7, 23].

Chronic Lyme borreliosis with joint involvement is characterized by persistent joint edema or recurrent inflammatory episodes. Immunological processes and genetic predisposition also play an important role in the pathogenesis of the disease. Patients positive for HLA-DR4 and HLA-DR2 antigens were shown to be more prone to chronic arthritis because of their cross-reaction with OspA antigen of spirochetes. The persistence of arthritis may be observed despite the eradication of spirochetes confirmed by currently available methods [6, 15, 20].

Chronic neuroborreliosis has a form of chronic progressive encephalomyelitis (more frequent in Europe), cognitive and memory impairment (more frequent in the US) and chronic peripheral neuropathy. In the case of medullary involvement, typical signs of progressive tetraparesis and/or paraparesis also develop. Cerebral nerve palsies (affecting nerves VII, VIII and IX-XII) are typical of Lyme borreliosis. Cognitive and memory impairment is characterized by impaired concentration and memory. It progresses slowly and may be accompanied by polyneuropathy [20, 24].

Post-Lyme syndrome is characterized by complaints and symptoms persisting more than 6 months after proper Lyme borreliosis treatment. In most cases musculoskeletal or radicular pain, dysaesthesia, neurocognitive symptoms, sleep abnormalities, and fatigue can be observed. The pathogenesis of post-Lyme syndrome is unclear and some physicians have questioned if this syndrome is an organic condition or rather a psychiatric disorder. Recent controlled studies do not support the use of additional antibiotics in these patients, but recommend primarily symptomatic strategies. Marques revealed a significant placebo effect in such patients, but this syndrome needs further study [12, 25, 26].

Diagnosis of Lyme borreliosis

Diagnosis of early Lyme borreliosis associated with EM needs no serological testing. It must be noted that EM usually appears within 2-30 days after the tick bite, while anti-Bb antibodies appear approximately 2-4 weeks after the initial tick bite. Thus, the patient with EM may have negative serological test results [2, 23].

The diagnosis becomes more difficult in disseminated disease. In such cases, careful epidemiological history confirming exposure to tick bites, typical signs and symptoms of Lyme borreliosis and positive tests for anti-Bb antibodies in the patient's serum form the basis of diagnosis. Serological testing is based on detection of antibodies against spirochetal antigens. Two-step diagnosis is necessary: the first step is based on a high sensitivity ELISA test, and positive results should later be confirmed by a more specific Western blot assay. Humoral response starts with IgM antibodies, which usually appear 2 to 4 weeks after infection. Their levels peak 8 to 10 weeks after infection and then gradually disappear, but in some patients may persist for several years. Immunoglobulin G (IgG) antibodies appear in serum 6 weeks after infection, reach their peak levels after 4 to 6 months and are detectable in serum for many years [20, 27, 28].

In patients where CNS borreliosis causes demyelination, anti-myelin antibodies are detected in the serum and cerebrospinal fluids (CSF). Imaging studies reveal disseminated demyelination of cerebral white matter, depicted as hypodense lesions in a computed tomography (CT) scan and disseminated hyperintense lesions in magnetic resonance imaging (MRI). The CSF analysis is helpful in the diagnosis of Lyme borreliosis in these cases. In meningitis the CSF cell count is increased to several dozen or several hundred cells per milliliter, accompanied by a slightly elevated CSF protein level and specific intrathecal IgG or IgM antibody synthesis, detected using the ELISA test. In the early stages,

Table I. Dosage and duration of Lyme disease treatment

Clinical picture	Suggested regimens	Dosage	Administration	Duration of the treatment [days]
EM BLC	Doxycycline	100 mg bid	po	14-21
	Amoxicillin	500 mg tid (children: 50 mg/kg/day)	po	14-21
	Cefuroxime	500 mg bid (children: 30 mg/kg/day)	po	14-21
Lyme disease with joint involvement	Amoxicillin	500-1000 mg tid (children: 50 mg/kg/day)	po	14-28
	Doxycycline	100 mg bid or 200 mg q24h	po	14-28
	Cefuroxime	500 mg bid (children: 15 mg/kg/day)	po	14-28
Lyme disease with nervous system, heart or recurrent joint involvement	Ceftriaxone	2000 mg q24h (children: 50-75 mg/kg/day)	iv	14-28
	Cefotaxime	2000 mg tid (children: 150-200 mg/kg/day: divided in 3-4 doses)	iv	14-28
	Penicillin G	3-4 mu q4h (children: 0.2-0.4 mu/kg/day divided in 4- 6 doses)	iv	14-28
ACA	Amoxicillin	500-1000 mg tid	po	14-28
	Doxycycline	100 mg bid or 200 mg q24h	po	14-28
	Ceftriaxone	2000 mg q24h	iv	14-28
	Cefotaxime	2000 mg tid	iv	14-28
	Penicillin G	3-4 mu q4h	iv	14-28

EM – erythema migrans, BLC – borrelial lymphocytoma cutis, ACA – atrophic chronic acrodermatitis, bid – twice a day, tid – 3 times a day, po – per os (by mouth), iv – intravenously, q4h – in each 4 h, q24h – in each 24 h

CSF abnormalities may be absent or minimal, and limited to a slight increase in protein levels [7].

Difficulties in serological testing may be a result of variation within individual *Borrelia* species, or in other words, different Bb antigen properties *sensu lato*. As a response to infection, and depending on the genospecies of the individual infecting strain, the patient can produce antibodies with a variable affinity to certain antigens and of substantial variability. Differences in the composition of those proteins in individual strains are of both a quantitative and qualitative character. Obtaining valid results of serological tests is impossible when using diagnostic antigen derived from only one strain. It is optimal to use recombinant antigens representing all *Borrelia* genospecies prevalent in a given territory [28].

Variable major protein-like sequence, expressed (VlsE) is a recently described marker which can improve diagnosis of Lyme borreliosis. One European multicenter study showed that in patients with erythema migrans, sensitivity for IgG antibodies increased from 47% to 66.8% when a new enzyme immunoassay (EIA) with recombinant VlsE from all three species combined with native *B. afzelii* antigen was used instead of a commercial EIA with native antigen [24, 29].

Treatment

Treatment of Lyme borreliosis in the phase of EM or borrelial lymphocytoma consists of doxycycline, amoxicillin or cefuroxime axetil. Arthritis is treated with oral doxycycline, amoxicillin or cefuroxime axetil, whilst neuroborreliosis, recurrent arthritis and heart involvement are treated with ceftriaxone, cefotaxime or penicillin G. The ACA is treated with amoxicillin, doxycycline, ceftriaxone, cefotaxime and penicillin G. Dosage and duration of treatment are summarized in Table I [16, 19, 20, 23].

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