

Musculoskeletal manifestations of Lyme borreliosis – a review

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Submitted: 12 November 2019; **Accepted:** 23 March 2020

Online publication: 17 June 2020

Arch Med Sci 2022; 18 (3): 726–731

DOI: <https://doi.org/10.5114/aoms.2020.96458>

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Abstract

Lyme borreliosis (LB) is a zoonotic disease caused by Gram-negative bacteria *Borrelia burgdorferi* sensu lato. The majority of reported cases of LB originate in the northern hemisphere, mostly in the US and Europe. One of the typical manifestations of LB are musculoskeletal symptoms; they may appear in any of the three LB stages. The diagnosis is based on clinical manifestations and confirmed by serological tests. One course of antibiotic therapy is sufficient for LB to dissipate in most cases, although for some patients, the symptoms subside gradually even after completion of therapy. Patients who have been demonstrated to have specific antibodies but are symptomless should not be treated. In instances where the advised treatment proved to be unsuccessful, patients should be referred to rheumatologist for additional diagnostics. The goal of this review is to update physicians on current scientific knowledge on musculoskeletal manifestations of LB.

Key words: *Borrelia*, diagnosis, Lyme arthritis, symptoms, treatment.

Introduction

Lyme borreliosis (LB) is a zoonotic disease caused by Gram-negative bacteria *Borrelia burgdorferi* sensu lato (*B. burgdorferi* s.l.), belonging to the *Spirochaetaceae* family. So far, at least 20 genospecies of spirochetes constituting the *B. burgdorferi* s.l. complex have been discovered, the pre-eminent pathogens being *B. burgdorferi* sensu stricto (*B. burgdorferi* s.s.), *B. afzelii*, and *B. garinii*; a few other species are considered nosogenic (*B. lusitanae*, *B. valaisiana*, and *B. spielmani*) [1, 2]. The last couple of years have been marked by a re-examination of spirochete taxonomy – the new classification and the name *Borrelia* have been established, but they have not been universally adopted [3, 4]. The vectors of *Borrelia burgdorferi* (Bb) spirochetes are ticks of the genus *Ixodes*. Pathogen transmission occurs during the bite of a tick consuming the host's blood [5]. A typical clinical picture of LB may include symptoms involving skin, joints, nervous system, and more rarely heart and eyes. Some infected patients are asymptomatic [1, 6]. The majority of reported cases of LB originate in the northern hemisphere, mostly in the US and Europe [7]. Clinical presen-

tation of LB includes three stages: early localised infection, early disseminated infection, and late disseminated infection [8]. This review is focused on musculoskeletal manifestations in LB, which will aid clinicians in diagnosis. Various musculoskeletal symptoms may be present in a wide array of conditions, while the presence of anti-borrelial antibodies in the general population could contribute to misdiagnosis. Lyme arthritis (LA) is one of the fundamental LB symptoms; it can be defined as the presence of arthritis with swelling and pain of one or several large joints, sometimes also pain in tendons, muscles, and/or bones in patients with serologically confirmed LB [2, 9, 10].

Pathogenesis of Lyme arthritis

Among the genospecies of Bb, *B. burgdorferi* s.s. demonstrates the strongest potential to damage joints [5]. It is the most common cause of LB in the United States; infection with this pathogen occurs in Europe much less commonly [5, 11, 12]. The basis of LA pathogenesis is a strong inflammatory reaction [1]. This reaction results in a perivascular collection of lymphocytes, macrophages, as well as scattered mast cells in the interstitium, typically found on histopathology in patients with severe LA [13]. Neutrophils, on the other hand, play a part in the initial phase of inflammation, subsequently being replaced by lymphocytes and plasma cells [14]. Inflammatory response of Th1 lymphocytes and cytokines: IFN- γ and, to a lesser extent, interleukin (IL)-4, IL-10, and IL-12 play an important role in LA [15]. There is mounting evidence that in addition to Th1 lymphocytes, Th17 cells are crucial in LA development. Synovial fluid of patients with LA contains IL-17-producing T cells as well as significantly higher IL-17 concentration than the control group [16, 17]. As mentioned earlier, the inflammatory reaction is paramount in LA development because Bb spirochetes do not produce toxins. However, recent studies have shown that Bbs express protease in aggrecanase activity, possibly contributing to direct damage to joint tissues. Aggrecan is a critical component of both the cartilage structure and the function of a joint [18]. Additionally, Bbs can influence the expression of a number of matrix metalloproteinases (MMPs), and aggrecanase ADAMST-4 in chondrocytes *in vitro*, MMP, and ADAMST-4 values are elevated in synovial fluid of LA patients [19–22]. It has been suggested that in an inflammatory reaction this leads to progressive degradation of aggrecan by host mechanisms, advancing chondral destruction and subsequent joint damage in LA [1].

Clinical picture

Musculoskeletal symptoms may appear in any of the three stages, even early localised infection,

often leading to miscategorisation of patients into the wrong stage.

In the early localised stage, during which *erythema migrans* (EM) is a classic symptom, some patients experience migratory muscle and joint pain. Nadelman *et al.*, in a prospective assessment of 79 patients with culture-confirmed EM, showed the presence of myalgia and arthralgia in almost half of the cases (correspondingly, 44% and 44%). Those symptoms are a non-specific reaction of the immune system to the infection and cannot function as a basis for diagnosis of LA [23].

In the next, early disseminated stage, arthritis may appear from a few days to months since the point of infection. The time between tick bite and the onset of LA may vary. In the US, in patients having exhibited EM and not treated with an antibiotic, LA developed in a period of 4 days to 2 years, 6 months on average; in Europe it was from 10 days to 16 months, 3 months on average [24, 25]. LA affects almost exclusively those not treated while EM was present or those who did not notice the EM altogether. Musculoskeletal symptoms in patients who had received prompt and appropriate treatment are extremely unlikely. Prompt treatment means starting antibiotic therapy before dissemination of infection, which usually occurs a few weeks (rarely – days) after the appearance of EM. Therefore, immediate antibiotic therapy in the first days of EM virtually eliminates the possibility of LB dissemination [1, 2]. LA constitutes approximately 28% of all forms of LB reported to CDC in the US [9]; that percentage is lower in Europe, reported as 4–8% in epidemiological studies [26–29]. Arthritis is the main component of LA, and arthralgia may precede, accompany, or follow the inflammation, and sometimes it can be the only rheumatic manifestation of LB; however, it should be considered a less common form of LA [5, 10]. In LA, usually there is one or few joints affected (oligoarthritis), normally no more than five, and involvement of many or most joints is atypical. Ordinarily, the joint involvement is asymmetrical and concerns mostly large joints, particularly the knee; small joints may be affected as a component of oligoarthritis, whereas an isolated involvement of small joints (e.g. of the hand) point to a cause other than LA. Apart from the knees, LA commonly affects the shoulder, elbow, wrist, and ankle joints [1, 2, 30–32]. Early research into the course of LA frequently noted involvement of the temporomandibular joint [24, 33]. According to Heir and Fein, it was the fourth most involved joint, following the knee, shoulder, and elbow [34]. However, in the following years that involvement was reported only sporadically, more often noting symptoms of temporomandibular disorders in the masticatory muscles [35–38]. The inflamed joints become swollen and painful; however, the pain

is not severe considering the exudate present in those joints. The skin above is warm but usually not red. Most patients report limited mobility in the affected joints, and some report fatigue or malaise, but other systemic symptoms are rare [1, 39, 40]. Typically, arthritis in the course of LB is accompanied by inflammation of the synovial membrane, and less often erosion and destruction of joint structures, which can be present in longer duration arthritis [41].

Symptom duration of at least 1 year allows diagnosis of the patient with chronic LB [8]. So far, few studies have attempted to assess long-lasting impairment of the musculoskeletal system years after treatment. Gerber *et al.*, in a prospective study of 90 children from the US, demonstrated that a few years after antibiotic therapy none of the children exhibited joint inflammation, while 4% suffered from mild to moderate musculoskeletal impairment, hindering physical activity [40]; a slightly larger percentage (8%) was observed in the European population [42, 43].

Diagnostic considerations

Diagnosis of LA must be started with a thorough history and examination of the patient. The history should contain information on: previous stays in tick-endemic regions, tick bites, length of time the tick had remained attached, and method of removal. It bears noting that approximately 27–42% of European patients do not remember the tick bite at the site of the EM, and up to 75% in the US; therefore, its absence in history does not exclude LB [6, 44–47]. The next diagnostic step is laboratory testing, performed only in patients whose reported symptoms correspond to the clinical picture of LB [1, 2].

Serology detects specific IgM, appearing in the blood 1–2 weeks after infection, peaking at 2–6 weeks, and specific IgG, appearing 2–6 weeks after infection, peaking at 4–6 months. The standard is two-tier serological testing in which the first step is a sensitive enzyme-linked immunosorbent assay (EIA). If the EIA is positive or equivocal, then separate IgM and IgG immunoblots should be performed. A positive immunoblot test with a positive or borderline EIA test confirms the presence of specific Bb antibodies. Because both the EIA and immunoblot may be falsely positive, it is not recommended to skip the first step (EIA) [1, 2, 8, 10]. When the symptoms are relatively recent (2–4 weeks) and serological testing is negative, it should be repeated after an additional 2 weeks [5, 30]. High antibody titre (IgM and IgG) may persist for many years, even with successful antibiotic therapy; therefore, serology does not differentiate between active infection and past infection or exposition to Bb in the past [1, 40]. With that

in mind, it is not recommended to test antibody levels post-treatment, given that they have no relation to the clinical picture of the disease [2].

The next diagnostic step in LA may be employing polymerase chain reaction (PCR), detecting DNA of Bb spirochetes in synovial fluid and/or membrane [10]. However, it has some constraints. The PCR test result will be positive in the presence of both alive and dead spirochetes. Its sensitivity for synovial fluid approximates 60–85%, meaning that a negative result does not exclude LA [1, 8, 10]. In the majority of patients pre-treatment, Bb DNA is usually found in the synovial fluid and the synovial membrane, whereas post-treatment with antibiotics, that result is usually negative [1, 5]. Synovial fluid itself is also employed in the diagnostic process of LA. It would be inflammatory, characterised by an increased WBC count, typically from 46,000/mm³ to 60,000/mm³ (in rare cases reaching more than 100,000/mm³) and dominated by neutrophils. It is usually collected to exclude other causes of arthritis, such as gout or bacterial arthritis. It is not recommended to use synovial fluid for *Borrelia* cultures [6, 47, 48]. Bb culturing is possible; however, the technique is expensive, requires additional laboratory conditions, and yields results after 2–6 weeks. Culturing Bb uses a rich BSK (Barbour, Stoenner, Kelly) medium and its modifications [49]. It is worth noting that a negative culture result does not exclude LB [10].

Complete blood count usually yields normal results for WBC, platelets, haemoglobin, and haematocrit. Only at an early stage of LA, in approximately 20% of patients in Europe, a small increase in aspartate transaminase and alanine transaminase may be observed. Every stage of LA may show a slight increase in erythrocyte sedimentation rate and/or C-reactive protein [5]. Medical imaging of the joints may reveal some essential data as well. Sonography or MRI might show fluid in the affected joint and thickening of the synovial membrane. X-rays of patients with chronic LA may show destruction of the joints, such as joint space narrowing, geodes, or erosion of cartilage; however, those signs are not LA specific and their prevalence is unknown. Therefore, having found joint deterioration, it is recommended to look for causes other than LA first [1, 41].

Serological methods used in diagnosing LB have their limitations. Seroreactivity after successful treatment of Lyme borreliosis may persist for years [8, 10]. Another diagnostic challenge is the possibility of false positive test results, possibly caused by cross-reactivity with other spirochaetal or bacterial antigens, as well as viral antigens, autoantigens [50–52]. Because using whole-cell lysates in ELISA is hindered by a greater possibility of cross-reactivity with other pathogenic bacteria, it is recommended that laborato-

ries use at least a second generation ELISA test based on a recombinant antigen, which decreases the likelihood of cross-reactivity. It is paramount to use multiple antigens typical only for pathogenic *Borrelia* strains and characterised by high binding ability to IgG and IgM [50]. Two-tier testing has low sensitivity in the early stages of the disease, due to the time needed for an immune response of the body, while the procedure itself is time-consuming. Therefore, several methods of one-tier testing, which would combine the speed and sufficient sensitivity in the early phase of LB, are being developed. Such tests are based on highly specific recombinant antigens or synthetic peptides for antibody detection. Moreover, using new assay platforms and analysers and multiplex assays fuels hopes for improvement of LB diagnosing, as presented in detail in an excellent review by Alasel and Keusgen [50].

Treatment

When musculoskeletal manifestations are present in patients with EM, the treatment is essentially the same as EM alone. First-line drugs include the following: doxycycline, amoxicillin, or cefuroxime orally. Dosing: doxycycline 100 mg every 12 h, amoxicillin 500 mg every 8 h, or cefuroxime 500 mg every 12 h – duration of treatment 14 days. In LA, however, that duration is longer, at 28 days. The dosing of doxycycline and cefuroxime is as given above; however, doses of amoxicillin are 500–1000 mg each 8 h. Second-line treatment in LA is IV ceftriaxone, 2 g every 24 h for 14–28 days. It has been established that if the symptoms subside only partially with oral antibiotic therapy, second-line treatment should consist of another recommended oral antibiotic, while reserving parenteral antibiotic treatment for those without any substantial clinical response [8, 10].

Untreated arthritis usually subsides on its own; however, it can take years – there have been cases where this form of LB persisted for 7–8 years [24, 53]. There is insufficient proof of effectiveness of additional antibiotic therapy courses; moreover, the potential side effects of such antibiotics need to be considered. Long-term antibiotic therapy, its frequent repetition, as well as combined therapy with multiple antibiotics, do not offer any benefit and should not be used [10, 30, 44, 54, 55]. At the start of therapy, approximately 7–30% of patients may experience aggravation of symptoms due to the Jarisch-Herxheimer reaction. It usually develops for 12–24 h from the start of treatment and is caused by sudden destruction of a large number of spirochetes. It does not require cessation of treatment and usually subsides in 48 h [56]. Pregnant and breastfeeding women should be

treated the same as the general population with the exception of doxycycline, which should not be used (as well as in children up to 8 years of age). Patients who have been demonstrated to have specific antibodies but are symptomless should not be treated [10].

Post-antibiotic Lyme arthritis

One course of therapy is sufficient for LA to dissipate in most cases, although for some patients the symptoms subside gradually even after completion of therapy; therefore, an assessment of outcome should be performed 3 months after its end. Some patients do not experience any improvement after antibiotic therapy; hence, the term ‘antibiotic-refractory LA’ was created, defined as persisting synovitis for > 1 month after two four-week oral antibiotic courses or > 2 months after completion of intravenous ceftriaxone treatment [8]. Risk factors of antibiotic-refractory LA remain not fully identified [1]. This form of persistent joint inflammation is now being called “post-antibiotic Lyme arthritis” (p-a LA), not to suggest antibiotic resistance as a cause of such a disease course [10]. There are two fundamental circumstances in which antibiotic therapy fails. The first is an erroneous diagnosis of LA, meaning a not uncommon situation where anti-Bb antibodies are found in a patient with musculoskeletal symptoms attributable to a different condition. Exclusion of other causes to the symptoms prompts us to consider the second option: p-a LA. The pathogenesis of p-a LA is not fully clear. The patients are characterised by a higher prevalence of HLA-DRB1*0401 and related alleles [57, 58]. A similar mechanism exists in rheumatoid arthritis, which suggests an autoimmune component to p-a LA [1]. Another idea is spirochete persistence. It has been demonstrated that in rare cases, Bb genetic material may be found in muscle tissue and synovial fluid many months after antibiotic therapy – PCR cannot, however, differentiate whether the genetic material comes from viable or non-viable organisms [59, 60]. Furthermore, as yet, no borrelial mRNA has been found in people with a positive PCR-DNA result, which suggests that DNA would come from non-viable spirochetes [61].

Therefore, it is recommended to initially, in instances where the above-mentioned treatment proves to be unsuccessful, for patients to be referred to rheumatologist for additional diagnostics and symptomatic treatment, and the search for other causes of symptoms should be considered [2, 10, 62, 63]. Possible methods of treatment for patients with p-a LA include the following: non-steroidal anti-inflammatory agents, disease modifying anti-rheumatic drugs (DMARDs), biologic agents, intra-articular steroids, and arthroscopic synovectomy [10].

Conflict of interest

The authors declare no conflict of interest.

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