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REVIEW

Clinical spectrum of Lyme disease

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Abstract

Lyme disease (borreliosis) is one of the most common vector-borne diseases worldwide. Its incidence and geographic expansion has been steadily increasing in the last decades. Lyme disease is caused by *Borrelia burgdorferi* sensu lato, a heterogeneous group of which three genospecies have been systematically associated to Lyme disease: *B. burgdorferi* sensu stricto *Borrelia afzelii* and *Borrelia garinii*. Geographical distribution and clinical manifestations vary according to the species involved. Lyme disease clinical manifestations may be divided into three stages. Early localized stage is characterized by erythema migrans in the tick bite site. Early disseminated stage may present multiple erythema migrans lesions, borrelial lymphocytoma, lyme neuroborreliosis, carditis, or arthritis. The late disseminated stage manifests with acordermatitis chronica atrophicans, lyme arthritis, and neurological symptoms. Diagnosis is challenging due to the varied clinical manifestations it may present and usually involves a two-step serological approach. In the current review, we present a thorough revision of the clinical manifestations Lyme disease may present. Additionally, history, microbiology, diagnosis, post-treatment Lyme disease syndrome, treatment, and prognosis are discussed.

Keywords Lyme disease · *Borrelia burgdorferi* · Tick-borne diseases · Ixodes · Erythema migrans · Lyme neuroborreliosis

History

The first description of clinical manifestations of Lyme disease (also known as Lyme borreliosis) was performed by Buchwald in 1883 describing atrophic skin lesions referring to them as diffuse idiopathic skin atrophy. These manifestations were renamed later by Herxheimer and Hartmann as atrophic chronic acrodermatitis in 1902. The characteristic erythematosus rash was first described by Swedish physician Afzelius in 1909 at a meeting of the Stockholm Dermatology Society and coined the term erythema migrans. Afzelius suggested the relationship with a tick bite in the region by *Ixodes reduvius*. In 1921, Afzelius published a six-case series, including the previous case, with the title Erythema Chronicum Migrans [1].

Garin and Bujadoux described a patient who presented erythema after a tick bite and subsequently pain, paralysis, and cerebrospinal fluid (CSF) pleocytosis [2]. In 1930, Hellerstrom reported a case which presented rash and posteriorly meningitis, establishing a link between both manifestations. The bacterial etiological agent was first hinted by Lenhoff who published in 1948 the presence of elements similar to spirochetes in erythema chronicum migrans skin biopsies. Posteriorly, Hellerstrom and Hollstrom successfully employed penicillin in erythema migrans with neurologic manifestations further supporting the infectious etiology theory [1].

An epidemic increase in cases of supposed "juvenile rheumatoid arthritis" in northeastern United States (US) alerted Yale researchers in 1975. Lyme disease was first described in 1977 detailing the findings of 51 residents of three contiguous Connecticut communities (Old Lyme, Lyme, and East Haddam) emphasizing the seasonal occurrence of cases and the geographic clustering [3]. Willy Burgdorfer and colleagues described in 1982 the finding of a spirochete in *Ixodes dammini* ticks. Additionally, serological analysis revealed that Lyme disease patients had higher antibody titers than controls further supporting this new microorganism (later named *Borrelia burgdorferi*) as the etiological agent [4].

Epidemiology

Lyme disease is present in America, Europe, and Asia, but most cases cluster in certain endemic regions. In North

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America and Europe, it is considered the most common vector-borne disease. Species of vector ticks differ in different geographic regions. *Ixodes scapularis* is the most frequent vector in the US. *I. pacificus* is probably the most important vector in western US. The incidence in the US has increased almost threefold from 1993 to 2013. Parallel to the increase in incidence, the geographic region has also expanded. The incidence in endemic states is 10–100 per 100,000 inhabitants. Underreport of Lyme disease is an important issue, and it is estimated that the true incidence is eightfold more than that reported [5].

In Mexico, serological assays have demonstrated a national seroprevalence of 1.1% [6]. Just as in the US, the highest prevalence (6.4%) was encountered in northeast states. [7]. Furthermore, *B. burgdorferi* has been isolated in tick vectors in many regions of northern Mexico [8].

Many countries in Europe are endemic for Lyme disease. The main vector is *I. ricinus*. Central and northeastern regions of Europe are the most affected. Different epidemiological reporting practices make incidence comparison between European countries difficult. *B. afzelii* is more frequently isolated in ticks from center and eastern regions, while *B. garinii* in western countries [5].

The main vector in Asian countries is *I. persulcatus* and it transmits *B. afzelii* and *B. garinii*. Several endemic areas are recognized in Russia and China. In the latter, Lyme disease has been confirmed in many provinces. The major endemic areas are located in northeast and northwest China [9]. Data on Lyme disease on the southern hemisphere is scarce although probable cases have been reported in countries such as Brazil and Australia [10].

Etiological agent

B. burgdorferi belongs to the phylum Spirochaetes and class Spirochaetae. This class contains several families including Spirochaetaceae and Leptospiraceae. Other human pathogens that belong to this class include *Treponema pallidum*, *Leptospira interrogans*, and *Borrelia recurrentis* causing syphilis, leptospirosis, and relapsing fever borreliosis, respectively. *B. burgdorferi* is a gram-negative bacterium with an approximate length of 20 to 30 micras and a width of 0.2 to 0.3 micras. It can be cultured in the Barbour–Stoenner–Kelly medium, but it is infrequently able to be recovered from human samples [2].

B. burgdorferi sensu lato (s.l.) is a heterogeneous group which contains 18 named genospecies. Of this, only three have been systematically and predominantly related to Lyme disease*: B. burgdorferi* sensu stricto (s.s.), *B. afzelii*, and *B. garinii*. Additionally, six other species have human pathogenic potential and some have been reported in human disease including *B. bissettii*, *B. spielmanii*, and *B. valaisiana* [11, 12].

The exact clinical spectrum of many *Borrelia* species is yet to be elucidated. The different species have variations in their vector and reservoirs, as well as in their geographic distribution. The most frequent specie in North America is *B. burgdorferi* s.s. while *B. afzelii*, *B. garinii*, and *B. burgdorferi* s.s. are all present in Europe [12].

The enzootic cycle is very intricate. Ticks of the *Ixodes ricinus* complex are mostly responsible for the transmission of Lyme disease. *I. scapularis* and *I. pacificus* are the main vectors in America and *I. ricinus* and *I. persulcatus* in Eurasia. Many animals participate as intermediate reservoirs, of which the white footed mouse (*Peromyscus leucopus*) is considered as the leading one. Other reservoirs include several species of small mammals like rats, squirrels, and shrews, and birds (which may contribute to dissemination of the disease) [13]. These ticks have a three-stage life cycle and acquire the bacteria by feeding on an infected reservoir [14]. Seasonality of reported cases suggests that ticks transmit the spirochete to humans predominantly during the nymph stage [5]. Although deer are incompetent hosts of *Borrelia* species, they represent an important role in Lyme disease because they are important feeding hosts of *Ixodes* ticks [5].

Clinical manifestations

Clinical stages

In a similar way to syphilis stages, Lyme disease clinical manifestations may be divided into three stages to simplify its diagnostic approach. The first one (early localized stage) is characterized by erythema migrans in the tick bite site. It occurs in the first weeks after the inoculation. The second stage (early disseminated stage) occurs weeks to months after the exposure and may manifest by multiple erythema migrans lesions, borrelial lymphocytoma, lyme neuroborreliosis, carditis, or infrequently, lyme arthritis. The third stage (late disseminated stage) manifests with acordermatitis chronica atrophicans, lyme arthritis, and neurological symptoms [15]. The presence of these signs and symptoms varies from between geographic regions and specific species.

Dermatologic manifestations

Erythema migrans, originally coined as erythema chronicum migrans by Azfelius, is the most frequent dermatologic manifestation of Lyme disease (Table 1). It is present in 70–95% of affected patients during the first 3 weeks of inoculation. It is more frequent in children than in adults. It presents as red to bluish-red, round or oval patch with centrifugal expansion that may present central clearing (Fig. 1). Some lesions have a target-like morphology (Fig. 2). It should measure 5 or more cm although maximum size is highly variable. Topography

Table 1 Dermatological manifestations

Erythema migrans
Borrelial lymphocytoma
Acrodermatitis chronica atrophicans (ACA)
Former association with morphea, Parry–Romberg syndrome, and lichen sclerosus
Lymphoma

varies depending on the bitten site. In children, the most common regions affected are head and neck, and in adult extremities or pelvis area [15]. Pruritus or a burning sensation is sometimes referred. Systemic symptoms such as malaise, lymphadenopathy, and fever may accompany erythema migrans. Without treatment, the lesions may persist for weeks to months. Infrequently, patients may present several erythema migrans lesions in this stage. Classic histopathological analysis was described as having a superficial and deep perivascular infiltrate with central eosinophils and peripheral plasma cells (Fig. 3). More recent reports reveal many and unspecific patterns including mild perivascular or periadnexal infiltrate with lymphocytes, neutrophils, plasma cells, or eosinophils. Some cases reveal an interface dermatitis or variable degrees of spongiosis thus highlighting the unspecific histopathologic picture which may difficult timely diagnosis [16].

Secondary erythema migrans presents as multiple lesions with similar characteristics to the original lesion although they tend to be less erythematous and edematous and may have an atypical morphology. The most frequent affected sites are the face and limbs. The distribution indicates spirochete dissemination via bloodstream or lymph [17].

Acrodermatitis chronica atrophicans (ACA) is a rare skin disease associated with late-stage Lyme disease. It is almost exclusively present in Europe where it affects around 10% of patients. Just as borrelial lympocitoma, most cases are caused by *B. afzelii* which may explain the geographical distribution

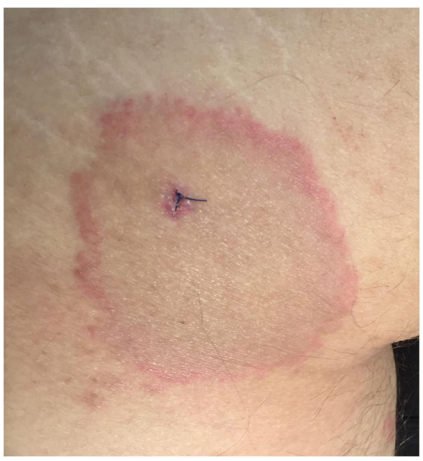

Fig. 1 Erythema migrans with erythematous border and central clearing

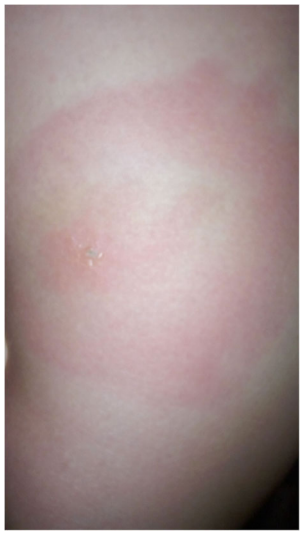

Fig. 2 Erythema migrans with target-like appearance with central crust 7 days after tick bite

of the reports. ACA is more frequent in older women has a predilection for the extensor surface of distal extremities [18]. The lesions begin as bluish-red plaques with edema that slowly progress throughout years to atrophic and hyperpigmented plaques with a skin appearance of "cigarette paper" [19]. This slowly progressing dermatosis culminates in severely atrophic skin with loss of adnexa and visibility of underlying blood vessels (Fig. 4). As it progresses, lesions may become bilateral or affect other extremities. More than 50% of patients report concomitant peripheral neuropathy with allodynia [20]. Histopathological analysis demonstrates a lymphocyte, plasma cells, and histiocytes perivascular and interstitial infiltrate with telangiectasia. Diagnosis may be hindered by presence of atypical features that may resemble granuloma annular, lichen sclerosus, or pseudolymphoma. Furthermore, recent reports have found new clinical presentations of ACA such as small violaceous patches, small spinous papules with erythema, and foot tumor [21, 22]. Diagnosis is often delayed several years because of the similarity of this entity with other diseases,

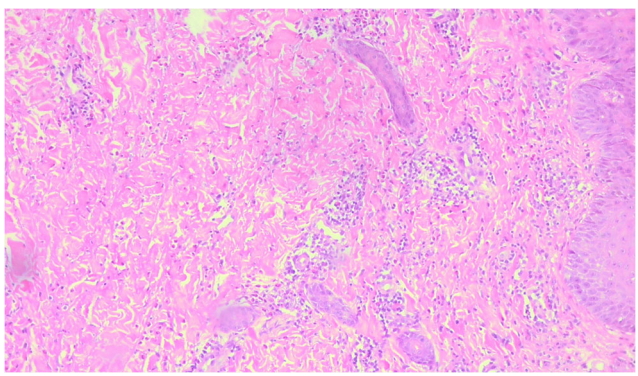

Fig. 3 Erythema migrans skin biopsy stained with hematoxylin and eosin (× 100) revealing superficial and deep dermal perivascular and periadnexal infiltrate with eosinophils and lymphocytes

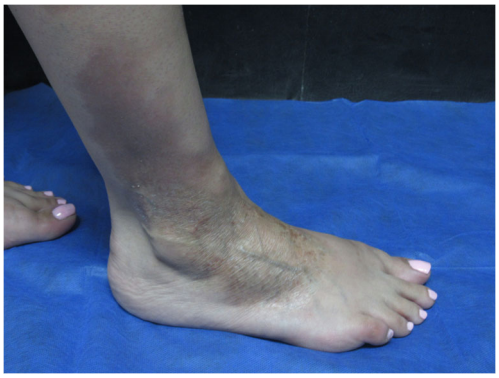

Fig. 4 Acrodermatitis chronica atrophicans secondary to *Borrelia afzelii* infection presenting with atrophic and hyperpigmented plaques with "cigarette paper" appearance

especially chronic venous insufficiency, and the ignorance of this late-stage presentation. Differential diagnosis includes other vascular diseases, morphea, lymphedema, and acrocyanosis.

Borrelial lymphocitoma is the rarest cutaneous manifestation of Lyme disease. It is almost exclusively reported in endemic regions of Europe and debuts weeks to months after initial erythema migrans or inoculation (usually 30–45 days after tick bite) [17]. The lesion is a single red or bluish puffy nodule measuring 1–5 cm. Children are most often affected usually on the earlobe. The breast or nipple is the most frequent reported site of borrelial lymphocityoma in adults. *B. afzelii* causes most borrelial lymphocitomas although *B. garinii*, *B. burgdorferi* s.s. and *B. bissettii* have also been reported [23]. Histopathology reveals an inflammatory lymphocytic infiltrate in the dermis with plasma cells and germinal centers [15]. Diagnosis is challenging in the absence of other clinical findings as it may mimic other lymphoproliferative lesions. The differential diagnosis is broad and includes lymphomas, lupus erythematosus, arthropod bite, and sarcoidosis. Biopsy is often necessary especially in non-endemic regions. Diagnosis may be confirmed my history of previous erythema migrans, serological assays, polymerase chain reaction (PCR), culture, or spirochete detection in the biopsy analysis.

Association of Lyme disease to other dermatologic conditions such as morphea, Parry–Romberg syndrome, lichen sclerosus, and lymphoma has been controversial. Some reports have found higher antibody positivity to *B. burgdorferi* in patients with linear scleroderma compared to the general population although some studies report opposing results [24, 25]. Parry-Romberg syndrome, also known as progressive hemifacial atrophy, has been linked to borrelial infection in few case reports, but coincidence of both diseases instead of causality or relationship cannot be ruled out. Lichen sclerosus is an infrequent condition of unknown etiology with some histological and clinical similarities to ACA and morphea. An Austrian study using focus-floating microscopy of 60 lichen sclerosus cases found positivity to *Borrelia* species in 63% compared to no detection in negative controls [26]. Lymphoma and other hematological malignancies, as well as solid tumors' relationship with Lyme disease is likewise still a matter of debate. The presence of many *Borrelia* species, the different spectrum of manifestations they cause, and varied detection techniques hinder adequate proof of relationship between these skin lesions and Lyme disease.

Lyme arthritis

Lyme arthritis is the second most common clinical finding in American patients. If left untreated, patients with EM develop arthritis in close to 60% of cases in an average time of 6 months. The arthritis is asymmetrical, monoarticular, or oligoarticular and may present in intermittent or persistent episodes. The most frequent affected joint is the knee. Periarticular involvement is frequent, and usually, less than five joints have synovitis in each episode. Characteristically, the joint swelling is severe, while the pain is moderate to mild. Serum white-blood cell count is usually within normal range, while inflammatory markers are usually high. Imaging study's findings are unspecific [27]. Arthrocentesis should always be performed in monoarticular arthritis to rule out septic arthritis or crystal arthropathy. Negative Gram staining and culture, absence of crystal detection in polarize light microscopy, negative serum rheumatoid factor, and anti-citrullinated protein antibodies should raise suspicious of Lyme arthritis. Synovial liquid white blood cell count ranges from 10,000 to 25,000 cells/mm^3. Anti-Borrelia antibody detection, history of previous erythema migrans, or PCR detection in synovial liquid warrant treatment. While most arthritis cases subside with adequate antibiotic treatment and non-steroidal anti-inflammatory drugs, chronic or erosive arthritis may develop [15, 20]. These complicated cases could benefit with treatment similar to other chronic inflammatory arthritis like methotrexate and hydroxychloroquine [27].

Lyme carditis

The term Lyme carditis groups the cardiovascular manifestations of Lyme disease. While relatively frequent in the 1980s, its prevalence has steadily dropped in Europe and North America. Additionally, changes in reporting and surveillance methodology have narrowed the reported prevalence. Cardiac involvement is reported in 1–2% of Lyme disease cases. Adult males correspond to most patients [28]. Lyme carditis presents in the second stage (early disseminated infection) 2–5 weeks after EM although it may occur even after a few days. Physicians should be aware of the cardiovascular signs and symptoms because of their potential mortality [18]. Symptoms include palpitations, syncope or pre-syncope, dyspnea, and chest pain. The most common manifestation of

Lyme carditis is cardiac conduction abnormalities. Atrioventricular (AV) block may rapidly progress to a third-degree one. A common finding is myocarditis and changes in surface electrocardiography. Diffuse myocardial involvement frequently results in ST segment changes [29]. Suspected Lyme carditis cases should be hospitalized and cardiac rhythm should be motorized. Colocation of temporary pacemakers is recommended in cases with hemodynamic instability, high-grade second- or third-degree AV block. Conduction abnormalities are reversible and resolve within a few weeks so permanent pacemakers are not recommended [28]. Other cardiac manifestations, although exceptional, include myocarditis, pericarditis, and acute heart failure (Table 2).

Table 2 Lyme carditis

Conduction disorders (predominantly atrioventricular block)
Palpitations
Syncope or pre-syncope
Dyspnea
Chest pain
Acute heart failure
Rarely pericarditis and myocarditis
Controversial association with dilated cardiomyopathy

Lyme neuroborreliosis

The neurologic manifestations of *B. burgborferi* infection usually present in the early disseminated stage (Table 3). Untreated EM patients develop Lyme neuroborreliosis (LNB) in 10–15% of cases. Timely treatment diminished this proportion. Prevalence of LNB varies from 12 to 14% in America to 16–23% in European patients. LNB has a slight preponderance in males and has a bimodal peak affecting children/adolescents and adults over 50 years [15]. During the early disseminated stage, American patients usually develop acute or subacute lymphocytic meningitis accompanied by headache and nuchal rigidity. The headache pattern is intermittent with periods of intense pain followed by mild pain. The pain if often referred in the frontal or occipital regions [30]. It may be accompanied by cranial neuritis, radiculoneuritis, or encephalitis. In recent case series, facial palsy has been the most common neurological manifestation in American LNB. The presentation is acute, usually unilateral, and more common in summer or fall months. A third of patients have concomitant CSF pleocytosis. Bilateral facial nerve involvement is found in a quarter of individuals [15, 31, 32]. LNB facial palsy is frequently misdiagnosed as Bell's palsy. History of tick bite, previous cutaneous lesions, children/adolescent cases, occurrence in summer/fall months and endemic areas, bilateral involvement, and CSF pleocytosis should raise awareness of the possibility of Lyme disease. Other cranial nerve involvement is (especially III, IV, V, and VI) exceptional [31]. In Europe, the most common clinical presentation is a painful meningoradiculitis known as Bannwarth's syndrome. It is mostly associated *with B. afzelii* infection. Common accompanying features are sharp pain that worsens at night, CSF lymphocytosis, sleep disturbances, headache, fatigue, paresthesia/paresia, facial palsy, and meningeal signs [32, 33].

Table 3 Lyme neuroborreliosis

• Early stage	• Late stage
- Cranial neuritis (usually facial palsy)	- Polyneuropathy (usually associated with acrodermatitis chronica atrophicans)
- Acute or subacute lymphocytic meningitis	- Chronic meningitis
- Bannwarth's syndrome	- Encephalitis
- Radiculoneuritis	- Myelitis
- Encephalitis	- Intracerebral hemorrhage
- Sleep disturbances	- Subarachnoid hemorrhage
- Headache	- Rarely associated with vasculitis or stroke
- Fatigue	
- Paresthesia/paresia	

Late LNB is outlined as persistent disease for 6 months or more. In the late disease stage, ACA may present polyneuropathy following the skin lesions. It has an asymmetric affection and sensory predominance secondary to axonal degeneration. Other late LNB manifestations include chronic meningitis, encephalitis or myelitis. It is of paramount importance to rule out other causes before establishing the definitive diagnosis of late LNB. *B. burgdorferi* antibody production should be demonstrated in CSF analysis [32]. Vasculitis central nervous involvement and stroke has been increasingly recognized as a late complication of Lyme disease. The spirochete has the potential to affect small and large blood vessels causing ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage. The myriad of clinical symptoms is similar to other causes and non-specific. Imaging studies do not confer specific Lyme disease findings. Intrathecal specific antibodies, CSF pleocytosis, and suggestive neurological symptoms support the diagnosis of *B. burgdorferi* infection [34].

Post-treatment Lyme disease syndrome

After appropriate antibiotic treatment, a variable number of patients may persist with symptoms mainly fatigue, musculoskeletal pain, and cognitive symptoms. These constellation of symptoms are grouped under the term post-treatment Lyme

disease syndrome (PTLDS) also sometimes referred as "chronic Lyme disease" [35].

The definition of PTLDS consist of the subjective symptomatology appearing in the first 6 months after diagnosis and treatment of adequately diagnosed Lyme disease and persistence of them for six or more months [18]. Persistent objective signs like Lyme arthritis or neurological sequelae like stroke or neuritis are not considered part of this group. Initial presentation with neurological involvement, treatment/diagnosis delay and severity of the infection are considered risk factors for PTLDS [35]. Persistence of *B. burgdorferi* infection in these patients has not been demonstrated. Furthermore, longer-term antibiotic schemes have not been proven to consistently improve health-related quality of life or symptoms in randomized control trials and have been linked to more drug-related adverse effects [36]. PTLDS is still a matter of debate and conclusive information about the higher prevalence of these symptoms than in the general population or other infections is lacking.

Diagnosis

Lyme disease diagnostic methods vary depending on the infection stage. A two-step assay is recommended by the Center for Disease Control. First, an enzyme immunoassay (EIA) or immunofluorescence assay (IFA) should be performed. Positivity of this test should warrant Western blot analysis, in which cases with symptomatology for ≤ 30 days should be tested for IgM and IgG and cases with symptomatology for > 30 days for IgG isotype [37].

EM can be diagnosed based on clinical findings including demonstrated or suspected tick bite or endemic site exposure. The expanding geographic area should be considered as new endemic regions have been recently recognized. Antibody assays are usually negative in the first weeks after infection. IgM isotype is positive in 20–50% of cases during the first 2–3 weeks. One to 2 months after infection, IgG is positive in most cases [18]. Borrelial lymphocytoma diagnosis is supported with a positive serology. Histopathology may help the diagnosis and is often performed to rule-out other similar conditions. Additionally, biopsy analysis by PCR or *Borrelia* culture may confirm the diagnosis although the sensibility of these tests is highly variable. ACA, just as other late disease stage clinical findings, is characterized by high-titer serum IgG antibodies. Reports of sero-negative ACA are exceptional. Histopathological analysis, PCR, or tissue culture may aid the diagnosis, although the high-titer assays are usually sufficient [38].

Lyme arthritis presents with high-titer IgG *Borrelia* antibodies. The two-tier diagnostic approach is highly sensitive (almost 100%) [39]. In cases where Lyme arthritis starts shortly after EM, IgG serology might be negative and it may be supplanted by PCR joint fluid evaluation [15]. Exclusion of other infectious or inflammatory arthritis is necessary. Synovial fluid analysis leucocyte count is in the inflammatory range, and Gram staining and bacterial cultures are negative. Rheumatoid factor and anti-cyclic citrullinated peptide antibodies are helpful to discard rheumatoid arthritis. In some cases, low-titer antinuclear antibodies are present.

Cardiovascular involvement in Lyme disease should be evaluated carefully to determine the time of inoculation or first symptoms. Cardiac conductance abnormalities during the first weeks after or during EM may have negative serology. The two-tier approach is recommended considering the days after symptom beginning. Recent neurological or cutaneous symptoms/signs compatible with Lyme disease support Lyme carditis diagnosis. Exceptionally, endomyocardial biopsy to demonstrate the spirochete by PCR or culture is indicated [38].

To establish the diagnosis of LNB, clinical manifestations and intrathecal specific antibody production are necessary. CSF pleocytosis is almost always present. Samples for antibody analysis must be taken simultaneously from blood and CSF to determine the CSF/serum antibody index and demonstrate central nervous system antibody production. In early LNB, intrathecal IgG should be positive in practically all patients as early as 6–8 weeks after symptoms begin [38]. Late LNB usually courses with high-titers antibody in serum and in CSF. Culture and PCR have a low yield in LNB but may be helpful in early, antibody-negative cases. A newer biomarker chemokine, CLCX13, is a promising tool but its employment is not routinely recommended. European guidelines determine definite cases as those fulfilling three of the following criteria: neurological symptoms, CSF pleocytosis and specific intrathecally produced antibodies. Possible LNB is defined as fulfilling two of the criteria mentioned [40].

Treatment and prognosis

Prevention of tick bites is encouraged to avoid Lyme disease. Use of protective clothing, frequent skin and cloth inspection, tick and insect repellent use, and prompt removal of attached ticks are endorsed. Antibiotic prophylaxis after a tick bite is only recommended when all the following criteria are fulfilled: local *B. burgdorferi* tick infection ≥ 20%, identification of adult/nymph *I. scapularis* tick suspected to be attached for ≥ 36 h; treatment can be started within 72 h after tick removal, no contraindication to doxycycline (children younger than 8 years old, pregnancy, breastfeeding). The only recommended scheme is a single 200 mg doxycycline dose in adults. Children 8 years old or older can receive a 4 mg/kg dose (maximum dose of 200 mg) [41].

The recommended oral regimens for Lyme disease are doxycycline 100 mg twice a day, cefuroxime 500 mg twice a day, and amoxicillin 500 mg every 8 h. Pediatric dosage is 4 mg/daily divided in two doses for doxycycline, 30 mg/kg divided in two doses for cefuroxime, and 50 mg/kg divided in three doses for amoxicillin. Maximum dosage for children

corresponds to the respective adult dose. The recommended parenteral antibiotic scheme is ceftriaxone 2 g/IV/daily (children dose of 50–75 mg/kg/daily, maximum dose of 2 g). As previously stated, doxycycline is contraindicated in children < 8 years, pregnancy, and breastfeeding [41]. Alternative oral and parenteral regimens include macrolides and cefotaxime/penicillin G, respectively.

Erythema migrans, borrelial lympochytoma, and cranial nerve palsy should receive an oral 14-day antibiotic regimen and ACA a 21-day one. For early LNB, besides solitary cranial nerve involvement, and late LNB, a parenteral 14-day regimen is indicated. Lyme arthritis without nervous system involvement warrants a 28-day oral antibiotic administration. Patients with recurrent arthritis after treatment, benefit from a second 28-day oral or parenteral scheme. If symptoms persist, other drugs should be considered including methotrexate or hydroxychloroquine. In monoarticular, recalcitrant patients, especially if the knee is the only joint involved, arthroscopic synovectomy is an option [27]. After the second Lyme carditis should be carefully monitored in specialized units. Temporary pacemaker should be considered in high-degree heart blocks. A parenteral antibiotic scheme should be timely administered which can be switched to an oral one after discharge to fulfill a total treatment time of 14 days [41]. PTLDS does not benefit from long-term antibiotics and adequate treatment strategies are still a matter of debate.

Prognosis of erythema migrans patients is excellent with > 90% returning to their previous health status. After treatment, LNB have a complete recovery in 70–85% of cases, particularly during the first year. Sequelae like paresis or neuropathic pain may persist in 5–28% of patients [15]. Antibiotic-resistant Lyme arthritis true incidence is unknown. It is estimated that around 90% of patients recover completely. Lyme carditis complications are acute in nature and chronic complications are exceptional. PTLDS statistics vary in reports due to methodological differences and enrollment. Recent studies found prevalence 10–20% [35]. Long-term outcome of PTLDS is not yet known.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained for iconographies.

References

1. Dammin GJ (1989) Erythema migrans: a chronicle. Rev Infect Dis 11(1):142–151
2. Herrera Lorenzo O, Infante Ferrer J, Ramírez Reyes C, Lavastida Hernández H (2012) Enfermedad de Lyme: historia, microbiología, epizootiología y epidemiología. Rev Cubana Hig Epidemiol 50: 231–244
3. Steere AC, Malawista SE, Snydman DR, Shope RE, Andiman WA, Ross MR et al (1977) Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. Arthritis Rheum 20:7–17
4. Burgdorfer W, Barbour AG, Hayes SF, Benach JL, Grunwaldt E, Davis JP (1982) Lyme disease-a tick-borne spirochetosis? Science 216:1317–1319
5. Mead PS (2015) Epidemiology of Lyme disease. Infect Dis Clin N Am 29:187–210
6. Gordillo G, Torres J, Solorzano F, Cedillo-Rivera R, Tapia-Conyer R, Munoz O (1999) Serologic evidences suggesting the presence of Borrelia burgdorferi infection in Mexico. Arch Med Res 30:64–68
7. Gordillo-Pérez G, Torres J, Solórzano-Santos F, Garduño-Bautista V, Tapia-Conyer R, Muñoz O (2003) Estudio seroepidemiológico de borreliosis de Lyme en la Ciudad de México y el noreste de la República Mexicana. Salud Publica Mex 45:351–355
8. Gordillo-Perez G, Vargas M, Solorzano-Santos F, Rivera A, Polaco OJ, Alvarado L et al (2009) Demonstration of Borrelia burgdorferi sensu stricto infection in ticks from the northeast of Mexico. Clin Microbiol Infect 15:496–498
9. Fang LQ, Liu K, Li XL, Liang S, Yang Y, Yao HW et al (2015) Emerging tick-borne infections in mainland China: an increasing public health threat. Lancet Infect Dis 15:1467–1479
10. Lopes FA, Rezende J, Silva D, Alves FCG, Oliveira CE, Costa IPD (2017) Molecular evidence of Borrelia burgdorferi sensu lato in patients in Brazilian central-western region. Rev Bras Reumatol Eng Ed 57:641–645
11. Rudenko N, Golovchenko M, Grubhoffer L, Oliver JH Jr (2011) Updates on Borrelia burgdorferi sensu lato complex with respect to public health. Ticks Tick Borne Dis 2:123–128
12. Stanek G, Reiter M (2011) The expanding Lyme Borrelia complex–clinical significance of genomic species? Clin Microbiol Infect 17: 487–493
13. Salkeld DJ, Leonhard S, Girard YA, Hahn N, Mun J, Padgett KA et al (2008) Identifying the reservoir hosts of the Lyme disease spirochete Borrelia burgdorferi in California: the role of the western gray squirrel (Sciurus griseus). Am J Trop Med Hyg 79:535–540
14. Radolf JD, Caimano MJ, Stevenson B, Hu LT (2012) Of ticks, mice and men: understanding the dual-host lifestyle of Lyme disease spirochaetes. Nat Rev Microbiol 10:87–99
15. Borchers AT, Keen CL, Huntley AC, Gershwin ME (2015) Lyme disease: a rigorous review of diagnostic criteria and treatment. J Autoinmun 57:82–115
16. Miraflor AP, Seidel GD, Perry AE, Castanedo-Tardan MP, Guill MA, Yan S (2016) The many masks of cutaneous Lyme disease. J Cutan Pathol 43:32–40
17. Vasudevan B, Chatterjee M (2013) Lyme borreliosis and skin. Indian J Dermatol 58(3):167–174
18. Steere AC, Strle F, Wormser GP, Hu LT, Branda JA, Hovius JW, Li X, Mead PS (2016) Lyme borreliosis. Nat Rev Dis Primer 2:16090. https://doi.org/10.1038/nrdp.2016.90
19. Godar DA, Laniosz V, Wetter DA (2015) Lyme disease update for the general dermatologist. Am J Clin Dermatol 16:5–18
20. Mullegger RR, Glatz M (2008) Skin manifestations of Lyme borreliosis: diagnosis and management. Am J Clin Dermatol 9: 355–368
21. Lenormand C, Jaulhac B, Debarbieux S, Dupin N, Granel-Brocard F, Adamski H et al (2016) Expanding the clinicopathological spectrum of late cutaneous Lyme borreliosis (acrodermatitis chronica atrophicans [ACA]): a prospective study of 20 culture- and/or polymerase chain reaction (PCR)-documented cases. J Am Acad Dermatol 74:685–692

22. Bauvin O, Schmutz JL, De Martino S, Busato T, Cribier B, Barbaud A et al (2017) A foot tumour as late cutaneous Lyme borreliosis: a new entity? Br J Dermatol 177(4):1127–1130
23. Maraspin V, Nahtigal Klevišar M, Ružić-Sabljić E, Lusa L, Strle F (2016) Borrelial Lymphocytoma in adult patients. Clin Infect Dis 63:914–921
24. Zinchuk AN, Kalyuzhna LD, Pasichna IA (2016) Is localized scleroderma caused by Borrelia burgdorferi? Vector Borne Zoonotic Dis (Larchmont, NY) 16:577–580
25. Gutierrez-Gomez C, Godinez-Hana AL, Garcia-Hernandez M, Suarez-Roa Mde L, Toussaint-Caire S, Vega-Memije E et al (2014) Lack of IgG antibody seropositivity to Borrelia burgdorferi in patients with Parry-Romberg syndrome and linear morphea en coup de sabre in Mexico. Int J Dermatol 53:947–951
26. Eisendle K, Grabner T, Kutzner H, Zelger B (2008) Possible role of Borrelia burgdorferi sensu lato infection in lichen sclerosus. Arch Dermatol 144:591–598
27. Arvikar SL, Steere AC (2015) Diagnosis and treatment of Lyme arthritis. Infect Dis Clin N Am 29:269–280
28. Robinson ML, Kobayashi T, Higgins Y, Calkins H, Melia MT (2015) Lyme carditis. Infect Dis Clin N Am 29:255–268
29. Scheffold N, Herkommer B, Kandolf R, May AE (2015) Lyme carditis–diagnosis, treatment and prognosis. Dtsch Arztebl Int 112:202–208
30. Marques AR (2015) Lyme neuroborreliosis. Continuum (Minneapolis, Minn). Neuroinfect Dis 21:1729–1744
31. Halperin JJ (2015) Nervous system Lyme disease. Infect Dis Clin N Am 29(2):241–253
32. Koedel U, Fingerle V, Pfister HW (2015) Lyme neuroborreliosis-epidemiology, diagnosis and management. Nat Rev Neurol 11:446–456
33. Ogrinc K, Lusa L, Lotric-Furlan S, Bogovic P, Stupica D, Cerar T et al (2016) Course and outcome of early European Lyme neuroborreliosis (Bannwarth syndrome): clinical and laboratory findings. Clin Infect Dis 63:346–353
34. Zajkowska J, Garkowski A, Moniuszko A, Czupryna P, Ptaszynska-Sarosiek I, Tarasow E et al (2015) Vasculitis and stroke due to Lyme neuroborreliosis - a review. Infect dis (London, England) 47:1–6
35. Aucott JN (2015) Posttreatment Lyme disease syndrome. Infect Dis Clin N Am 29:309–323
36. Berende A, ter Hofstede HJ, Vos FJ, van Middendorp H, Vogelaar ML, Tromp M et al (2016) Randomized trial of longer-term therapy for symptoms attributed to Lyme disease. N Engl J Med 374:1209–1220
37. CDC (1995) MMWR Morbidity and mortality weekly report. Recommendations for test performance and interpretation from the Second National Conference on Serologic Diagnosis of Lyme Disease. https://www.cdc.gov/mmwr/preview/mmwrhtml/00042555.htm .Accesed 10 July 2018
38. Stanek G, Fingerle V, Hunfeld KP, Jaulhac B, Kaiser R, Krause A et al (2011) Lyme borreliosis: clinical case definitions for diagnosis and management in Europe. Clin Microbiol Infect 17:69–79
39. Shapiro ED (2014) Lyme disease. N Engl J Med 370(18):1724–1731
40. Mygland A, Ljostad U, Fingerle V, Rupprecht T, Schmutzhard E, Steiner I (2010) EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. Eur J Neurol 17:8–16
41. Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS et al (2006) The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 43:1089–1134