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The clinical diversity of Lyme disease – diagnostic and therapeutic challenges

1. Weronika Matera

ORCID: 0009-0008-4942-2112 weronika.matera00@gmail.com

University Clinical Hospital of Wroclaw Medical University, Borowska 213,

50-556 Wrocław

2. Zuzanna Kalinowska

ORCID: 0009-0005-3940-3987 zuzanna.kalinowska@student.umw.edu.pl

Lower Silesian Centre for Oncology, Pulmonology and Haematology

plac Hirszfelda 12, 53-413 Wrocław

3. Hanna Aleksandrowicz

ORCID : 0009-0006-3686-3942

hania.aleks24@gmail.com

Lower Silesian Centre for Oncology, Pulmonology and Haematology

plac Hirszfelda 12, 53-413 Wrocław

4. Olga Krężel

ORCID: 0009-0007-5687-3440 olgkrezel@gmail.com

4. Military Clinical Hospital and Polyclinic IPHC

Weigla 5, 53-114 Wrocław

Corresponding author:

Olga Krężel

725565789

olgkrezel@gmail.com

ul. Pułaskiego 36/85

50-446 Wrocław

Abstract

Lyme disease is the most common tick-borne disease in Europe, including Poland, where it is endemic and poses a growing public health issue. Caused by *Borrelia burgdorferi sensu lato*,

it is characterized by a wide variety of clinical presentations, which makes it difficult to diagnose correctly. The aim of this study was to analyze the available scientific data on the classic course of Lyme disease and its atypical and asymptomatic forms, as well as to draw clinicians' attention to the diagnostic complexity of this disease. A systematic review of the literature was conducted using PubMed, Google Scholar, and Web of Science databases, covering publications in Polish and English. The results of the analysis indicate that Lyme disease can manifest itself in many forms, ranging from typical erythema migrans, through arthritis and neuroborreliosis, to rare skin and cardiac forms. Asymptomatic cases, which may affect up to 7% of infected individuals, pose a particular challenge. In this group of patients, specific antibodies are present in the absence of clinical symptoms of the disease, and current guidelines do not clearly define the principles of therapeutic management. The lack of characteristic symptoms, limitations of serological tests, and complex clinical course contribute to both delayed diagnosis and overdiagnosis of the disease. The results of the review indicate a need for further research on standardizing diagnostics and developing clear criteria for treating patients with asymptomatic Lyme disease.

Objective

The aim of this study was to analyze the diversity of manifestations of tick-borne Lyme disease in comparison to its typical course, according to available scientific publications, as well as to draw clinicians' attention to how problematic and complex it can be to make a correct diagnosis in a patient with atypical Lyme disease.

Materials and methods

The article presents a systematic review of scientific studies on the classic course of Lyme disease and its diagnosis, as well as specific forms of clinical manifestation of this disease. For this purpose, selected articles were analyzed using the PubMed, Google Scholar, and Web of Science databases. In addition, the bibliographies of the cited works were reviewed to verify the references. Both Polish and English-language literature was used. The bibliography search and article selection took place in June 2025.

Keywords

Lyme disease, zoonosis, *Borrelia burgdorferi*, Ixodes ricinus, ELISA, erythema migrans

Introduction

Lyme disease remains one of the most common tick-borne diseases both in Europe and in Poland, where it is endemic. It is a progressive, multisystemic disease caused by *Borrelia burgdorferi sensu lato* spirochetes, with the symptoms most commonly caused by *B. burgdorferi sensu stricto*, *B. afzeli*, and *B. garini*, which are pathogenic genospecies. In Poland, infections with *B. afzeli* and *garini* are predominant. The bacteria are transmitted by ticks of the genus Ixodes. According to data from the National Institute of Public Health, the number of cases has been steadily increasing since the end of the COVID-19 pandemic, reaching 29,347 in 2024, compared to 25,244 cases in 2023 [1]. Lyme disease is diagnosed when the following criteria are met: characteristic symptoms, epidemiological history (recent contact with a tick, staying in endemic areas) and positive serological test results based on two-stage diagnostics (stage I - ELISA, stage II - Western blot). If only one of the above conditions is met—positive serological test results—a suspected asymptomatic infection may be diagnosed. This is a condition in which, despite the absence of symptoms specific to Lyme disease, reactive antibodies against *B. burgdorferi* are detected by serological methods. Currently, there are no clear guidelines on the management of patients with asymptomatic Lyme disease, nor are there precise criteria for its diagnosis. In this paper, we present a review of the available literature in an attempt to answer the question of whether asymptomatic patients should be diagnosed and treated.

Discussion

a. Basic information

Lyme borreliosis (LB) is a vector-borne zoonosis transmitted by ticks of the genus Ixodes (in Europe, most commonly *Ixodes ricinus* [2]). These ticks undergo a four-stage life cycle: egg, larva, nymph, and adult, feeding on blood only once during each active stage. Unfed ticks attach to the host's skin by means of specialised mouthparts and, after several days of feeding—approximately 3 days for larvae, 5 days for nymphs, and 7 days for adult females—they detach from the host and move to the surface of the soil or its vicinity to continue their development.

Human infections are caused by pathogenic spirochaetes of the *Borrelia burgdorferi sensu lato* complex, among which *Borrelia garinii*, *Borrelia afzelii*, *Borrelia burgdorferi sensu stricto*, and *Borrelia spielmanii* are most frequently isolated.

Transmission occurs during the tick's feeding through the injection of saliva into the host's skin. In order for Borrelia spirochaetes to be transmitted, a sufficiently long feeding period is generally required, ranging from approximately 17 to 36 hours, depending on the tick species and Borrelia genospecies involved [3–6]. Therefore, prompt and proper removal of attached ticks from the skin is of key preventive importance [7].

Throughout their life cycle, ticks parasitise a variety of animal species, enabling the transfer of bacteria to successive hosts, including humans, and contributing to the persistence of the pathogen in the environment [8]. In endemic regions such as Poland, transmission of Lyme borreliosis can occur both in suburban areas and in rural regions used for forestry and recreational purposes [9].

b. Epidemiology

Owing to climatic changes, including global warming, milder and shorter winters, and long, often humid summer seasons, combined with the growing popularity of outdoor recreation and tourism, there has been a dynamic increase in the incidence of tick-borne diseases, primarily Lyme borreliosis [10].

A study based on the reimbursement data from the Polish National Health Fund (NFZ) demonstrated that between 2008 and 2016 an average of 119.6 cases of Lyme borreliosis requiring medical intervention were reported per 100,000 person-years [11]. However, as noted by G. Brestrich et al., official epidemiological data considerably underestimate the true number of LB cases in Poland. During the same period, the National Institute of Public Health reported a much lower incidence—30.9 per 100,000 person-years—suggesting that for each case registered in the national surveillance system, there were approximately 2.7 cases requiring medical care. Applying this ratio to the years 2021–2023, when 48.5 cases per 100,000 person-years were officially reported, yields an estimated true incidence of 130.9 per 100,000 person-years, corresponding to approximately 49,644 cases annually across the country [12].

The most recent data from 2024, according to the NIPH (NIZP) report, indicate an official incidence of 78.13 per 100,000 population (29,347 newly registered cases), representing an increase compared to the previous year (67.07 per 100,000) [1].

Lyme borreliosis is endemic throughout Poland, with notable regional differences in incidence. According to Paradowska-Stankiewicz et al., the highest incidence was recorded in the eastern and north-eastern provinces—Podlaskie, Lubelskie, and Warmińsko-Mazurskie—where the annual average ranged from 78.8 to 115.2 cases per 100,000 inhabitants [13]. This may be attributed to the greater forest cover and extensive agricultural areas characteristic of these regions.

Furthermore, LB is diagnosed slightly more frequently in women (55.7% of cases), with the highest incidence observed in the 65–69 age group [13].

The average annual incidence of Lyme borreliosis in Poland is higher than that reported in neighbouring countries such as the Czech Republic (37.3/100,000 in 2007–2016), Germany (33/100,000 in 2013–2017), and Belarus (25.5/100,000 in 2019) [14–16], yet lower than in some Northern and Eastern European countries, such as Finland (99.6/100,000 in 2015–2020) and Lithuania (85.4/100,000 in 2014–2016) [17]. Nevertheless, inter-country comparisons remain difficult due to differences in epidemiological surveillance systems (including mandatory case reporting) and case definitions based on divergent diagnostic strategies.

c. Clinical Presentation

Lyme borreliosis is a multisystem disease that most commonly affects the skin, joints, nervous system, and heart. Its clinical spectrum includes both acute and chronic forms, and the diversity of symptoms is attributed to the various Borrelia genospecies responsible for infection [18]. The heterogeneous global distribution of these species contributes to regional variation in clinical presentation. For instance, in Europe, where B. garinii and B. afzelii predominate, involvement of the nervous system and skin is considerably more frequent than in North America [19].

In terms of clinical manifestations observed in Poland, the most common are erythema migrans (EM) and Lyme arthritis (LA). According to Polish studies, EM accounted for approximately 74% of all cases and LA for about 32%. Neuroborreliosis (LNB) was less frequent, with an

incidence of 0.8 per 100,000 inhabitants, representing approximately 1.7% of all cases [13], consistent with the findings of Brestrich et al. [12].

- Skin

Erythema migrans (EM) is the most common and one of the earliest manifestations of Lyme borreliosis, occurring in approximately 30–60% of infected individuals (in some studies 60–80% [20]) and typically appearing within 3–30 days after a tick bite [19,21]. The lesion initially presents as a small red macule or papule, gradually expanding peripherally to form the characteristic erythema. In its classical form, EM appears as a red ring with a well-defined, intensely coloured border and central clearing ("bull's-eye" appearance) [19]. However, the appearance of EM may vary, depending also on the Borrelia genospecies involved [22].

EM may be the only sign of infection, yet it is frequently accompanied by non-specific systemic symptoms such as malaise (54%), myalgia and arthralgia (44% each), headache (42%), and fever or subfebrile states (39%) [19]. In some cases (approximately 2–18%), multiple EM lesions (EM multiplex) may develop as a result of haematogenous or lymphatic dissemination of spirochaetes. These secondary lesions are usually smaller than the primary erythema and often lack central clearing [22].

In untreated patients, EM may persist for several weeks, typically around 4 weeks but occasionally up to 12 weeks. Although it can resolve spontaneously, lack of antibiotic treatment increases the risk of complications and late manifestations of Lyme borreliosis. Importantly, the absence of EM in medical history does not exclude LB, as not all infected individuals develop or recognise the lesion [19,22,23].

Borrelial lymphocytoma (BL) is a rare early manifestation of LB, occurring in less than 1% of infected individuals—most frequently in children. It represents a local immune response to Borrelia burgdorferi infection and is classified among benign B-cell pseudolymphomas [24]. The lesion presents as a well-demarcated, firm, non-tender nodule with a bluish-red or violaceous colour, most commonly located on the ear lobe, nipple, or scrotum, and less frequently on the neck [25]. It may appear alone or in association with EM, either preceding or coinciding with it, and regional lymphadenopathy is occasionally observed. Diagnosis requires serological and histopathological confirmation. BL follows a benign course and usually resolves within several weeks of antibiotic therapy [25,26].

Acrodermatitis chronica atrophicans (ACA) is a rare late manifestation of Lyme borreliosis, occurring predominantly in Europe, most often in women and older adults. It affects approximately 1–3% of infected individuals, with Borrelia afzelii being the principal causative agent [27]. Skin lesions develop slowly over months or even years after untreated EM, typically involving the extremities but also the face or trunk. Early lesions present as bluish-red discolouration, swelling, telangiectasias, and hyperpigmentation. A characteristic feature may include the so-called "blue toe," denoting swelling and cyanosis of a digit. During the atrophic phase, the skin becomes thin, parchment-like, and pale, with epidermal flattening and dermal fibrosis due to the degradation of elastic fibres. Neurological symptoms such as pruritus, burning sensations, paraesthesia, and pain—related to peripheral neuropathy—are common [19].

Unlike other forms of LB, ACA does not resolve spontaneously. Lesions may persist for years, and molecular or culture-based tests (e.g., PCR) can confirm active infection. Despite its chronic course, ACA responds well to antibiotic treatment [28]. Diagnosis requires both serological evidence of Borrelia antibodies and histopathological confirmation of inflammatory changes in skin biopsy specimens [29].

- Joints

Lyme arthritis (LA) typically develops several weeks to months (up to six months) after infection and manifests with musculoskeletal pain. It most commonly presents as a monoarthritis or oligoarthritis, primarily affecting large joints—particularly the knees, ankles, hips, elbows, and wrists—though small joints of the hands and feet may occasionally be involved [19,30].

Clinically, joint swelling is often asymmetric and accompanied by pain and local warmth. The disease course may be relapsing–remitting; however, in untreated cases, symptoms can persist for months or years. In some patients, even despite treatment, persistent inflammatory changes such as tenosynovitis or bursitis may occur, requiring additional anti-inflammatory management [19]. Untreated acute arthritis may evolve into a chronic form, leading to irreversible joint destruction [30,31].

- Nervous System

Neuroborreliosis (NB) is a manifestation of LB involving pathological changes in both the central and peripheral nervous systems. Neurological manifestations occur in approximately 10% of LB patients [32] and may appear during either the early (early NB) or late (late NB) phases of the disease.

In early NB, symptoms develop within days to weeks after a tick bite and include meningitis, cranial neuritis—most commonly facial nerve (cranial nerve VII) palsy, unilateral or bilateral—and, less frequently, involvement of other cranial nerves causing diplopia, pain, hearing loss, or vertigo [33]. Peripheral nerve and radicular inflammation (radiculoneuritis) is also characteristic, producing neuropathic pain radiating along dermatomes and often associated with sensory deficits and muscle weakness [34].

Early NB is more common in children, who usually present with facial palsy, while in adults it more frequently manifests as radiculoneuritis accompanied by lymphocytic pleocytosis in cerebrospinal fluid [33]. The early phase may also involve lymphocytic encephalitis. When meningitis, cranial neuritis, and radiculoneuritis occur simultaneously, this clinical triad—known as Bannwarth's syndrome—is pathognomonic for NB [19,33,35].

Late NB, defined by symptom duration exceeding six months, may present with chronic neurological manifestations such as peripheral symmetrical polyneuropathy, mononeuritis multiplex, chronic encephalitis, myelitis, or meningitis. These may be associated with cognitive impairment, including memory and concentration difficulties, drowsiness, and irritability. In rare cases, stroke-like symptoms may occur as a result of cerebral vasculitis [35,36].

- Cardiovascular System

Cardiac involvement (Lyme carditis, LC) occurs in approximately 5% of LB patients. Due to earlier diagnosis and more effective treatment, cases of LC have become increasingly rare. This form may present as myocarditis, pericarditis, or endocarditis, as well as with conduction abnormalities such as atrioventricular block and bundle branch block. Atrial fibrillation and tachyarrhythmia have also been reported. Most patients, however, remain asymptomatic, with diagnosis based primarily on ECG changes (particularly atrioventricular block) [37,38].

LC most commonly affects younger individuals, particularly men, presenting with syncope or a prolonged PQ interval exceeding 300 ms. Although LC is usually self-limiting, untreated cases may result in serious complications, including cardiomyopathy [39].

Diagnosis of Lyme borreliosis is often challenging due to its heterogeneous clinical presentation and non-specific systemic symptoms, such as chronic fatigue, episodic neck pain (so-called Dontha's sign), thermoregulatory disturbances, alcohol hypersensitivity, and sensory or cognitive impairments involving hearing and vision [40]. Furthermore, laboratory diagnostic and interpretative difficulties may lead to overdiagnosis and the irrational use of antibiotics in suspected LB cases [41].

Lyme disease diagnosis

Diagnosis and treatment of Lyme disease are based primarily on the observation of characteristic clinical symptoms and confirmation of infection through serological tests. An exception is erythema migrans - an "early" skin lesion that in some cases is the first symptom of the disease. In such instances, it serves as the basis for initiating treatment and does not require additional diagnostic tests [42]. In cases where it is not observed and there is no history of tick bites in the patient's medical history, diagnosis of the disease can be difficult due to the multitude of various symptom combinations in patients [43]. In this instance, laboratory tests are helpful.

There are two main types of diagnostic tests:

- direct methods, which analyse the presence of antigen or DNA of the spirochetes in the patient's blood

- indirect methods, i.e., serological analysis, which defines the patient's response to infection [44].

Nevertheless, they should not be used as screening tests for Lyme disease in the general population due to the high number of false positive results. They may, however, be considered for people who are professionally exposed to ticks, such as foresters [45].

Indirect methods

Over the past two decades, there has been significant development in serological testing technology and methodology, and to this day, they remain the most frequently used and easiest diagnostic tool.

Serological diagnosis of Lyme disease is carried out similarly in most European countries and in the United States [46]. The guidelines standardised a two-stage diagnostic protocol to maximise clinical sensitivity in the first stage and specificity in the second [47]. The first diagnostic step is a quantitative assessment of specific antibodies against spirochetes in blood serum. The serum is analysed using an ELISA immunoenzymatic test. Less commonly, IFA immunofluorescence tests or MMIA multiplex tests are used for this purpose. A negative result

of these tests suggests that infection is unlikely and the patient does not require further testing in the second stage. However, if the clinical picture supports the diagnosis, retesting may be considered [48].

Positive or equivocal results require verification by the Western Blot technique. The serum sample is analysed using standardised IgM and IgG immunoblots. The test detects antibodies directed against specific Borrelia proteins. Further interpretation of the result depends on the duration of the disease. In the third to fourth week of the disease, IgM antibodies appear, mainly directed against the flagellin p41 protein and the OspC protein. Over time, the immune response expands [49].

A positive IgM antibody result alone – without an accompanying positive IgG result – should not be regarded as confirmation of active Lyme disease in patients whose symptoms persist for more than a month. If seroconversion does not occur within 30 days, the result is likely a false positive [50]. This may be due to non-specific cross-reactions in the IgM class. These occur, among other things, in autoimmune diseases or diseases caused by other spirochetes, as well as during infection with EBV or CMV [51].

Serological diagnostics also have certain limitations in the case of early forms of the disease. This is due to the delayed immune response after infection. For this reason, early diagnosis of Lyme disease may be difficult in the acute phase of the disease. On the contrary, in late forms, such as chronic atrophic dermatitis (ACA) or neuroborreliosis, the patients' serum usually shows a strong antibody response [52].

After infection, IgG antibodies may remain in the blood of patients for many years. For this reason, monitoring their concentration after treatment is not justified. It is also not recommended to test people without any symptoms, as a positive test result may only indicate past exposure to B. burgdorferi [45].

Direct methods

In many infectious diseases, direct diagnosis, which involves identifying the pathogen itself, is considered the most reliable way to confirm active infection. Direct methods include, among others, culturing the microorganism, microscopic analysis, detection of the pathogen's genetic material, and detection of its antigens. However, these methods are of limited use in the case of Lyme disease [53].

Bacterial culture

Culture is a difficult and impractical diagnostic tool. The bacterial growth process is slow and requires special media, specialised equipment, and qualified personnel. In addition, samples

often contain very few live bacteria - sometimes too few to detect. For these reasons, *Borrelia* culture is currently not recommended as a routine diagnostic method [54].

Polymerase chain reaction (PCR)

Detection of *B. burgdorferi* genetic material using standard PCR, real-time PCR, or NGS methods enables rapid and early laboratory diagnosis of infection even before an immune response develops. However, the PCR method cannot distinguish between active and past infection, as spirochete DNA can persist for weeks or months after treatment [55]. It also detects dead bacteria or their residual DNA, and the low number of live microorganisms in samples may lead to false-negative results [56]. Sensitivity is significantly higher in cerebrospinal fluid or synovial fluid than in blood. Due to these limitations, indirect methods continue to be used as the first line of treatment.

On the other hand, it is a rapidly developing method. Promising results have been achieved with new PCR methods such as Phage-PCR (phage test) – a new method that detects only live bacteria, based on the presence of DNA from viruses that multiply only in active infections (e.g., the Phelix Phage test) [57].

Antigen detection tests

They are rarely used and not very reliable in clinical practice. The main problem is the very low quantity of bacteria or antigens in body fluids, which depends, among other things, on the stage of the disease and the type of sample. These methods are still in the clinical trial phase and are considered to be auxiliary procedures [58].

Asymptomatic Lyme disease

Erythema migrans (EM) is undoubtedly the most common symptom which indicates infection with *Borrelia* spirochetes. However, proper classification of erythema migrans remains a challenge for both clinicians and patients. Due to the wide variety of its possible appearances and forms, this skin lesion is often misjudged, leading to incorrect diagnosis and inaccurate treatment.

In the United States, approximately 80% of EM cases appear as a uniform red patch, while only about 20% take on the characteristic “bull’s-eye” or target-like pattern. Typically, the lesion is circular, but its shape may vary depending on its location. Atypical features of EM include central induration, blistering, or necrosis, which can make it resemble spider bites.[59]

It is estimated that around 16% of patients with early Lyme disease do not present the typical symptoms such as erythema migrans. In these individuals, the first manifestations are often nonspecific, viral-like symptoms — fever, malaise, fatigue, and general weakness.

Among patients with untreated Lyme disease, about 18% report complaints such as fatigue, joint pain, and muscle pain, yet without developing the classical neurological manifestations characteristic of the late stage of the disease.

Patients with a positive IgG fraction against *Borrelia* and flu-like symptoms may in fact represent cases of Lyme disease, forming a considerable subgroup among patients presenting with ambiguous symptoms.

The term *probable Lyme disease*, defined as a positive IgG result accompanied by subjective complaints, remains controversial. Aucott J. et al. argue that initiating treatment in such patients is unlikely to result in significant clinical improvement. Therefore, many researchers advocate against screening for Lyme disease in patients presenting with nonspecific symptoms that do not provide a strong indication for *Borrelia* infection testing.[60]

Asymptomatic Lyme disease continues to pose a challenge for researchers. Up to 7% of Lyme disease cases may remain asymptomatic, and prognosis for this group is generally favorable. Allen C. et al. conducted a Lyme vaccine study involving 269 participants. Among them, 11% were classified as patients who underwent asymptomatic seroconversion. This group also included individuals who were not entirely symptom-free but exhibited nonspecific, hard-to-classify symptoms. Most of these patients were treated after seroconversion against *Borrelia* antibodies had been documented.

Treatment was withheld in eight patients, and one of them developed arthritis approximately one year after seroconversion. These findings suggest that truly asymptomatic patients do not require treatment, and if the infection does not resolve spontaneously, it will eventually manifest with recognizable clinical symptoms.[61,62]

Summary

Lyme disease is the most common tick-borne disease in Europe and Poland, where it is endemic. The number of cases is steadily increasing—in 2024, over 29,000 new cases were reported. The

symptoms of the disease are varied, which makes diagnosis difficult and contributes to both overdiagnosis and delays in appropriate treatment.

Asymptomatic Lyme disease poses a particular challenge – some patients have antibodies but no typical symptoms. It is estimated that up to 7% of infected individuals are asymptomatic, usually with a good prognosis. Currently, there are no clear guidelines for the treatment of such individuals, and most studies suggest that routine treatment in this group is not necessary. Asymptomatic Lyme disease poses a diagnostic and clinical challenge, and its role in the development of later manifestations of the disease requires further study.

Disclosure

Author's contribution:

Conceptualization: Weronika Matera, Zuzanna Kalinowska, Hanna Aleksandrowicz, Olga Krężel

Methodology: Weronika Matera, Zuzanna Kalinowska, Hanna Aleksandrowicz, Olga Krężel

Formal analysis: Weronika Matera, Zuzanna Kalinowska, Hanna Aleksandrowicz, Olga Krężel

Investigation: Weronika Matera, Zuzanna Kalinowska, Hanna Aleksandrowicz, Olga Krężel

Writing - rough preparation: Weronika Matera, Zuzanna Kalinowska, Hanna Aleksandrowicz, Olga Krężel

Writing - review and editing: Weronika Matera, Zuzanna Kalinowska, Hanna Aleksandrowicz, Olga Krężel

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