International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

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ARTICLE TITLE	LYME DISEASE AND THE GREAT IMITATOR: DIFFERENTIAL DIAGNOSIS IN COMPLEX CLINICAL PRESENTATIONS. LITERATURE REVIEW
DOI	https://doi.org/10.31435/ijitss.3(47).2025.4058
RECEIVED	26 August 2025
ACCEPTED	28 September 2025
PUBLISHED	30 September 2025
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LYME DISEASE AND THE GREAT IMITATOR: DIFFERENTIAL DIAGNOSIS IN COMPLEX CLINICAL PRESENTATIONS. LITERATURE REVIEW

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ABSTRACT

Introduction and objective: Lyme disease is a tick-borne zoonosis caused by the bacterium Borrelia burgdorferi, characterized by highly variable and often nonspecific manifestations. Its ability to mimic neurological, rheumatological, cardiological, and psychiatric disorders makes it a classic"great imitator." The aim of this review is to summarize current knowledge on the differential diagnosis of Lyme disease and to highlight the risks associated with both under- and overdiagnosis.
Brief description of the state of knowledge: Despite its prevalence, the literature rarely addresses Lyme disease comprehensively as a"great imitator." Most studies focus on selected organ-specific manifestations, and reports of atypical or misleading cases are scarce. This review integrates data on symptoms—particularly neurological, rheumatological, and cardiological—providing a framework for understanding diagnostic challenges. It emphasizes the overlap of clinical presentations with other diseases and the limitations of current diagnostic methods, highlighting the need for more integrated approaches in clinical practice and research.
Methods: A literature review was conducted using PubMed and Google Scholar with
search terms like"Lyme disease", "Lyme carditis", "Lyme arthritis", "Neuroborreliosis" and related variations. Articles published within the last five years were prioritized.
Conclusions: Lyme disease should always be considered in patients with unexplained, multi-organ symptoms, but diagnosis must rely on rigorous clinical and laboratory criteria. Awareness of its ability to mimic other conditions is essential to avoid missed or misattributed diagnoses. Diagnostic vigilance and critical interpretation of results are key to optimizing patient care and preventing therapeutic errors.

KEYWORDS

Lyme Disease, Lyme Carditis, Lyme Arthritis, Neuroborreliosis, Great Imitator

CITATION

Karina Grzesik, Katarzyna Pilarczyk, Aleksandra Rabęda. (2025) Lyme Disease and the Great Imitator: Differential Diagnosis in Complex Clinical Presentations. Literature Review. *International Journal of Innovative Technologies in Social Science*. 3(47). doi: 10.31435/ijitss.3(47).2025.4058

Introduction

Lyme disease is a zoonosis occurring primarily in Europe and North America. It is caused by the spirochete Borrelia burgdorferi, whose predominant vector in Europe is the tick Ixodes ricinus. Most ticks become infected by feeding on blood from B. burgdorferi reservoirs, which include small mammals and birds [1]. In Europe, where B. garinii and B. afzelii are the predominant species, involvement of the nervous system and skin is observed more frequently than in North America, due to the differing organ tropism of individual Borrelia species [2]. Lyme disease is classified into three stages: early localized, early disseminated, and late. Lyme disease and its therapeutic implications represent an increasing global health concern due to the rising incidence of infections over the past two decades. The clinical presentation, pathophysiology, and epidemiology of the disease are well characterized, and treatment of early and late stages is based on 10–14-day and four-week courses of doxycycline, respectively [3, 4]. The initial stage typically presents with erythema migrans—a characteristic expanding skin lesion at the site of the tick bite—often accompanied by nonspecific systemic symptoms such as fever, headache, muscle and joint pain, and general malaise. In most patients, the disease remains limited to this stage. Approximately one-fifth of patients progress to the disseminated stage, characterized by multiple skin lesions and neurological, ophthalmic, and cardiac manifestations, including cranial nerve palsies (especially of the facial nerve, cranial nerve VII), meningitis, and cardiac conduction abnormalities. In the late stage of Lyme disease, arthritis is the most common manifestation, usually presenting as oligoarthritis primarily affecting large joints, particularly the knees [5, 6].

Table 1. Symptoms of Lyme disease at its various stages

Early Lime disease	
Early localized stage	- erythema migrans - borrelial lymphocytoma - flu-like symptoms
Early disseminated (systemic) stage	- arthritis, mild myositis - lymphocytic meningitis, cranial neuritis - Garin-Bujadoux-Bannwarth syndrome (meningo-polyradiculoneuritis) - carditis - multiple erythema migrans
Late Lime disease	
- radiculoneuritis - chronic encephalomyelitis - meningoencephalitis - acrodermatitis chronica atrophicans - chronic fatigue - bursitis or tenosynovitis	

Lyme disease, due to its nonspecific and multisystemic manifestations, poses a significant diagnostic challenge in daily clinical practice. Its course can mimic numerous conditions, including autoimmune, neurological, rheumatological, and psychiatric disorders, often leading to delays in establishing the correct diagnosis. In some cases, Lyme disease may also mask coexisting illnesses, further complicating their identification and management [7, 8]. The aim of this review is to discuss the most common diseases considered in the differential diagnosis of Lyme disease and to highlight potential diagnostic pitfalls that may result in misdiagnosis and inappropriate therapeutic decisions.

Diagnostic challenges

The diagnosis of Lyme disease remains a controversial issue, primarily due to the discrepancy between the approach based on objective clinical criteria and laboratory confirmation of Borrelia burgdorferi infection, and the view that allows diagnosis based solely on nonspecific symptoms without etiological verification. Scientific evidence does not support the latter perspective, which promotes overdiagnosis and the use of unvalidated diagnostic methods that frequently yield false-positive results [9]. The diagnosis of Lyme disease

is based on a two-tier serologic algorithm—an initial ELISA (EIA) followed by confirmatory Western blot testing for IgM and IgG antibodies [10]. While this method offers high specificity, its sensitivity is limited in the early phase of infection, particularly within the first month. Therefore, in the presence of characteristic erythema migrans, the diagnosis should be made clinically without waiting for serologic confirmation [10, 11]. Moore et al., in their review paper, compiled data on the sensitivity and specificity of serological tests used in patients with suspected Lyme disease in the United States [12]. Based on the presented data, there are significant differences in the sensitivity of serologic tests used in the diagnosis of Lyme disease depending on the disease stage and the diagnostic algorithm applied. In the acute phase of early Lyme disease with erythema migrans (EM), the standard two-tiered algorithm using whole-cell sonicate ELISA shows low sensitivity: 40% and 38% [13, 14], whereas the two-EIA algorithm demonstrates higher sensitivity—53% and 58%. Sensitivity increases during the convalescent phase, reaching 63% and 67% with the two-EIA approach, compared to 61% or as low as 27% with the classic algorithm. For noncutaneous manifestations, such as neuritis or carditis, the sensitivity of all algorithms is significantly higher, reaching 100% or 95–96%, confirming their clinical utility in more advanced stages of the disease. In summary, serologic tests show limited sensitivity in the early phase of Lyme disease but maintain high specificity, particularly in disseminated disease. Algorithms based on two EIA tests appear slightly more sensitive in early infection compared to the classic CDC-recommended two-tiered algorithm, which may be clinically relevant for early Lyme diagnosis [13, 14, 15]. The early stage of Lyme disease can be particularly challenging to diagnose due to its nonspecific clinical presentation and the reduced sensitivity of serologic tests during this phase. Diagnosis is further complicated by the fact that the clinical picture often mimics other conditions, such as viral infections, rheumatologic disorders, or neurological syndromes. This necessitates a high degree of clinical suspicion, careful epidemiological assessment, and thorough patient history [12, 16].

Another challenge in Lyme disease diagnostics is the overuse of serological tests without consideration of clinical presentation and epidemiological history. Data from seven major commercial laboratories in the US showed that in 2008 approximately 3.4 million tests were performed on 2.4 million samples, incurring costs of around $492 million. Although most testing (≥62%) adhered to the recommended two-tier algorithm, the estimated proportion of truly infected patients ranged only from 10% to 18.5% [17]. Another research study focused on the overuse of serological testing in the diagnosis of Lyme disease analyzed 18,410 tests performed at U.S. Air Force healthcare facilities between 2013 and 2017. Of the 1,352 IgM immunoblots performed, 249 (18.4%) were positive. After excluding repeat tests, insufficiently documented cases, and patients with a history of Lyme disease, 212 positive cases were evaluated. In 113 of them (53.3%), the result was determined to be a false positive. Antibiotics were administered to 97 out of 99 individuals with a true-positive result (98.0%) and to 91 out of 113 individuals with a false-positive result (80.5%) [18]. In a retrospective cohort study conducted by Kobayashi et al. (2000–2013), 1,261 patients referred to a Mid-Atlantic academic medical center for suspected Lyme disease were evaluated. The vast majority (84%) showed no clinical or laboratory evidence of active Borrelia burgdorferi infection. Notably, 65% of these patients received alternative diagnoses, with 59% being newly identified medical conditions, while the remaining cases were attributed to pre-existing health issues. A total of 139 distinct clinical diagnoses were identified as potential explanations for the patients' symptoms. The most common diagnoses included anxiety and depression (21%), fibromyalgia (11%), chronic fatigue syndrome (7%), migraine disorder (7%), osteoarthritis (6%), and sleep disorders, including obstructive sleep apnea (5%). Less frequent, but clinically significant diagnoses included multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis (ALS), sarcoidosis, and various malignancies. The median symptom duration among the cohort was 796 days [8]. The findings indicate a high rate of Lyme disease misdiagnosis and emphasize the necessity of rigorous differential diagnosis in patients with chronic symptoms. Excessive testing and misinterpretation of results highlight the need to integrate clinical and epidemiological data with serology to improve diagnostic accuracy [17, 18].

Differential diagnosis

Lyme disease, due to its broad spectrum of nonspecific clinical manifestations, is considered one of the classic "great imitators," alongside conditions such as syphilis and systemic lupus erythematosus. The disease can present with symptoms affecting nearly every organ system, which may lead to misdiagnosis or delayed recognition. Diagnostic challenges are particularly prominent in cases of neuroborreliosis, Lyme arthritis, and chronic pain or fatigue syndromes, as these may clinically mimic a wide range of autoimmune, infectious, or psychosomatic disorders [19]. A particularly common challenge in the diagnosis of Lyme disease is the clinical scenario in which there is no history of a tick bite or erythema migrans, yet symptoms typical of later stages of the disease are present—symptoms that are also common in many other clinical conditions [7].

Lyme carditis

Ozgur et al. reported a case of a 31-year-old woman with Lyme carditis, a rare manifestation of Lyme disease in which Borrelia burgdorferi affects the heart muscle, most commonly causing conduction abnormalities and less frequently myocarditis, pericarditis, or symptoms mimicking myocardial infarction. When symptomatic, the most common manifestations include fatigue, shortness of breath, dizziness, syncope, and palpitations [20]. The patient presented with chest pain, shortness of breath, and fatigue. Laboratory tests showed significantly elevated troponin levels (8712 pg/mL) and electrocardiography (ECG) changes consistent with STEMI. Coronary angiography revealed no atherosclerotic lesions, and the diagnosis was confirmed by serological evidence of active B. burgdorferi infection [21]. Atypical case of Lyme carditis was described in a case report by Najam et al. It involved a 70-year-old male with a history of hypertension and calcific bicuspid aortic stenosis who presented to the emergency department with worsening exertional dyspnea and orthopnea. Initial laboratory tests revealed leukocytosis (white blood cells (WBC) 16.6 $\times 10^9$/L), anemia (haemoglobin (Hb) 9.3 g/dL), elevated Erythrocyte Sedimentation Rate (136 mm/h), increased creatinine (2.6 mg/dL), and elevated Brain Natriuretic Peptide (877 pg/mL). ECG showed bradycardia and a first-degree atrioventricular (AV) block. Physical examination revealed jugular venous distension, a systolic murmur over the aortic area, and bilateral lower limb edema. Echocardiography confirmed moderate aortic stenosis with a left ventricular ejection fraction of 50–55%. The exercise stress test was terminated due to dyspnea, accompanied by hypotension and ischemic ST segment changes. Given the endemic nature of Lyme disease in the patient's region, a tick-borne disease panel was performed, which confirmed infection with Borrelia burgdorferi and Ehrlichia chaffeensis [22]. Mensah et al. reported the case of a 52-year-old woman with a history of hypertension and Chronic Obstructive Pulmonary Disease (COPD), who complained of dyspnea, fever, chills, fatigue, and arthralgia. Clinical evaluation revealed bradycardia, hypotension, and T-wave flattening in the precordial leads on ECG. Chest imaging showed bilateral pulmonary edema and interstitial infiltrates, while echocardiography demonstrated newly diagnosed mild left ventricular systolic dysfunction. Coronary Computed Tomography Angiography (CTA) revealed no evidence of coronary artery disease. Serologic testing confirmed infection with Borrelia burgdorferi [23]. The presented cases of Lyme carditis demonstrate that the disease can manifest with atypical clinical features beyond the classic atrioventricular block. Symptoms such as heart failure, nonspecific ECG changes, or wall motion abnormalities may obscure the diagnosis, especially when they occur outside the typical tick exposure season and without a clear history of a tick bite. In such scenarios, it is advisable to include Lyme disease in the differential diagnosis, even in the absence of typical risk factors, particularly in populations from high-incidence regions [21,22,23].

Lyme arthritis

Lyme arthritis is a late manifestation of Lyme disease, presenting as recurrent inflammation of large joints, most commonly the knee, caused by a prolonged immune response to Borrelia burgdorferi. It can mimic other rheumatic diseases, making diagnosis challenging [24]. In the case series described by Unlu et al., data from six adult male patients aged 32 to 78 years with a final diagnosis of Lyme arthritis (LA) were analyzed. All patients presented with unilateral knee arthritis, and in two cases, the wrist joint was also affected. A history of tick bite was reported in five patients, while none recalled the presence of erythema migrans. The duration of symptoms prior to diagnosis ranged from 2 to 38 months (mean: 12 months), indicating significant diagnostic delays. In all cases, Borrelia burgdorferi DNA was detected in synovial fluid by PCR, and serological testing revealed positive IgG antibodies; IgM antibodies were present in four patients. All patients had previously received intra-articular corticosteroid injections, and three had also been treated with methotrexate, suggesting an initial suspicion of autoimmune rheumatic disease. Only after the diagnosis of LA was established was antibiotic therapy initiated (ceftriaxone, doxycycline, or a combination of both), resulting in clinical improvement [25]. In the study by Stevenson et al., a case of a 25-year-old man presenting with acute inflammatory swelling of the left knee is described. Despite multiple joint aspirations, intra-articular steroid injections, and treatment with disease-modifying antirheumatic drugs, the patient experienced recurrent arthritis flares over 10 months, leading to bone erosions on imaging. History revealed prior residence in an area endemic for Lyme disease in upstate New York, USA, though he did not recall any tick bites or erythema migrans rash. Serological tests confirmed Borrelia antibodies (positive ELISA and IgG immunoblot), and Borrelia DNA was detected in the synovial fluid [26]. While the cases described by Unlu et al. and Stevenson et al. focused on adult patients with advanced Lyme arthritis (LA), Cruz et al. conducted a retrospective analysis in a pediatric population to identify clinical and laboratory parameters distinguishing three clinically similar conditions: Lyme arthritis (LA), septic arthritis (SA), and transient synovitis (TS). All three can present

with hip pain and joint effusion but differ significantly in etiology and therapeutic approach. The study reviewed data from 93 children who underwent hip joint aspiration at a tertiary care children's hospital located in a Lyme-endemic region. LA was diagnosed in 17 patients, SA in 40, and TS in 36. Multivariable logistic regression revealed that a history of fever (OR = 16.3; 95% CI: 2.35–113.0) and elevated peripheral white blood cell (WBC) count (OR = 1.26; 95% CI: 1.01–1.58) were significantly associated with SA compared to LA. In contrast, an elevated erythrocyte sedimentation rate (ESR) (OR = 1.06; 95% CI: 1.02–1.10) increased the likelihood of LA compared to TS. These findings highlight the diagnostic utility of basic clinical and laboratory markers in differentiating LA from other causes of isolated hip effusion in pediatric patients [27]. These observations confirm that Lyme arthritis, in both pediatric and adult populations, can clinically mimic other conditions, including autoimmune arthritis and bacterial joint infections. The variability of clinical presentation and absence of pathognomonic features contribute to significant diagnostic challenges and delays in initiating appropriate therapy. [24, 25, 26, 27]. In contrast to previously discussed reports highlighting atypical and delayed presentations of neuroborreliosis, the study by Barclay et al. offers an important perspective on the issue of Lyme disease overdiagnosis. The authors analyzed 11 cases in which patients were diagnosed with "Lyme arthritis" based on Borrelia burgdorferi immunoblot testing of synovial fluid. In 91% of cases, the diagnosis was incorrect—patients did not meet established criteria for Lyme arthritis, were seronegative (unlike the nearly universal seropositivity observed in late-onset Lyme arthritis), and the synovial fluid profile was inconsistent with typical Borrelia-associated inflammatory patterns. Antibiotic therapy failed to yield clinical improvement in all but one patient who met confirmed diagnostic criteria. This study serves as a critical warning against the use of non-validated diagnostic methods and underscores that not only delayed diagnosis but also overinterpretation of questionable results may lead to misdiagnosis, unnecessary antibiotic use, and delays in appropriate management [28].

Neuroborreliosis

Among the various clinical forms of Lyme disease, neuroborreliosis holds a distinct position due to its variable symptomatology, nonspecific course, and capacity to mimic numerous neurological and psychiatric disorders. Involvement of the central or peripheral nervous system by Borrelia burgdorferi may occur in both early and late stages of the disease, often in the absence of a previously identified erythema migrans or recollection of tick exposure. Neuroborreliosis is frequently misdiagnosed as multiple sclerosis, Guillain-Barré syndrome, viral meningitis, demyelinating diseases, and even psychiatric conditions such as depression, anxiety, or chronic fatigue syndrome [29]. Melia et al. emphasize that while neuroborreliosis commonly affects the facial nerve, isolated hearing loss or optic neuritis are rare and poorly documented manifestations of Borrelia burgdorferi infection. Case analyses from endemic regions show that patients presenting with chronic neurological symptoms such as headache, dizziness, or subjective cognitive complaints rarely exhibit confirmed central nervous system inflammation. These nonspecific symptoms can occur in both healthy individuals and those with other conditions. The authors highlight the importance of careful interpretation of such symptoms in the context of Lyme disease to avoid overdiagnosis and unnecessary antibiotic treatment [30]. Sayad et al. reported the case of a 55-year-old man admitted with new-onset generalized tonic-clonic seizures and impaired consciousness requiring intubation. The patient's symptoms had started one week earlier with mild headache, low-grade fever, malaise, anorexia, and vomiting. Cerebrospinal fluid analysis revealed lymphocytic pleocytosis and elevated protein levels consistent with aseptic meningitis. Given the patient's occupation as a butcher and positive yet inconclusive serologic results for brucellosis, neurobrucellosis was initially considered—a differential diagnosis relevant due to its overlapping neurological manifestations and CSF findings. However, molecular and further serologic testing failed to confirm brucellosis, and subsequent serology demonstrated IgM and IgG antibodies against Borrelia burgdorferi, establishing the diagnosis of neuroborreliosis. Intravenous ceftriaxone therapy resulted in significant clinical improvement [31]. Rana et al. described the case of a 58-year-old woman in whom Lyme neuroborreliosis presented in an atypical and diagnostically challenging form, closely mimicking a range of other neurological and internal medicine conditions. The patient was admitted to the emergency department with dizziness, gait ataxia, slurred speech, and tremors, without fever or other infectious symptoms. A few days earlier, she had sought medical care for lumbar spine pain and had been treated with nonsteroidal anti-inflammatory drugs. On physical examination, the only notable finding was bilateral upper extremity dysmetria, with no focal neurological deficits or rash. An initial suspicion of stroke led to urgent neuroimaging (CT and MRA), which showed no abnormalities. Significant electrolyte disturbances were identified, including hyponatremia (116 mEq/L), hypokalemia (2.5 mEq/L), hypochloremia (68 mEq/L), and hypoosmolality (252 mOsm/kg), which directed the workup toward

a metabolic cause. However, the emergence of bilateral lower limb weakness and paresthesia during hospitalization raised concern for spinal pathology or Guillain-Barré syndrome. MRI of the lumbar and thoracic spine showed only degenerative spondylosis and chest imaging ruled out paraneoplastic syndrome. After discharge, the patient returned ten days later with worsening lower extremity symptoms and altered mental status. In the context of persistent hypoosmolar hyponatremia and new neurological findings, Lyme neuroborreliosis was suspected. Serological testing revealed significantly elevated IgM and IgG antibodies to Borrelia burgdorferi, confirmed by a positive Western blot in serum and cerebrospinal fluid (CSF) [32]. Jarosińska and colleagues presented a case of a 64-year-old male with a history of hypertension, hyperlipidemia, emphysema, and prior pulmonary embolism, admitted for acute respiratory failure worsening in the supine position and cervical spine pain. Initial imaging studies, including chest and cervical spine CT scans, brain MRI, and bronchoscopy, excluded pulmonary embolism, pneumonia, central nervous system pathology, and airway abnormalities. Chest X-ray revealed elevation of the left hemidiaphragm, and fluoroscopy demonstrated bilateral phrenic nerve palsy. During the differential diagnosis, other conditions were systematically excluded: myasthenia gravis was ruled out based on negative electromyography and absence of anti-acetylcholine receptor and anti-MuSK antibodies; autoimmune neurological disorders were excluded by negative anti-ganglioside, anti-MOG, and anti-aquaporin antibody tests; viral infections (HSV, CMV) and syphilis (negative VDRL) were also ruled out. Guillain-Barré syndrome was considered due to neurological symptoms, but no confirmatory findings were present. Serological testing revealed elevated IgM and IgG antibodies against Borrelia burgdorferi in serum, while cerebrospinal fluid analysis detected oligoclonal bands and positive Western blot antibodies, confirming Lyme neuroborreliosis as the underlying cause of bilateral phrenic nerve palsy [33]. The authors reported the case of a 62-year-old woman who presented to the emergency department with a two-day history of weakness in the left hand and both legs, accompanied by falls resulting in head trauma. The patient reported a temporal association between symptom onset and recent stressful events, as well as a self-limited episode of diarrhea three weeks prior. Initial laboratory tests and head computed tomography were unremarkable, and the patient was discharged. The following day, she returned with worsening motor symptoms, tetraparesis, and urinary incontinence. Neurological examination revealed asymmetric tetraparesis, hyporeflexia, ambiguous sensory disturbances, and a positive Babinski sign on the left side. Imaging studies showed microangiopathic changes in the cerebral white matter and degenerative cervical spine changes without evidence of spinal cord compression. Cerebrospinal fluid analysis revealed elevated protein concentration (0.57 g/L) with a normal cell count and negative infectious tests (syphilis, CMV, EBV). Based on albuminocytologic dissociation and electromyography results, Guillain-Barré syndrome was suspected, and a five-day course of intravenous immunoglobulin (0.4 g/kg/day) was initiated, resulting in partial improvement. Further diagnostics revealed positive IgM antibodies against Borrelia burgdorferi (IgG negative) in serum, lymphocytic pleocytosis (20/μL) in cerebrospinal fluid with normal protein levels, and a confirmatory immunoblot test, establishing a diagnosis of neuroborreliosis. The patient did not recall any tick bites or skin changes. A 14-day course of intravenous ceftriaxone was started, after which significant improvement in motor function was observed [34]. In a prospective study conducted by Briciu et al. at an academic referral center in Cluj-Napoca, Romania, the differential diagnosis and clinical-serological response to antibiotic treatment were evaluated in 42 patients hospitalized with suspected Lyme neuroborreliosis (LNB). According to the European diagnostic criteria (neurological symptoms, cerebrospinal fluid pleocytosis, and intrathecal production of Borrelia burgdorferi-specific antibodies), none of the patients fulfilled all three criteria necessary for a definite diagnosis of LNB. Only 16.6% (n=7) were classified as possible LNB (meeting two out of three criteria), while LNB was excluded in 78.6% (n=33). During follow-up, three patients were diagnosed with alternative neurological disorders (multiple sclerosis or amyotrophic lateral sclerosis) that mimicked LNB and coexisted with nonspecific IgM seropositivity. Additionally, 30% (11/36) of the patients maintained a positive IgM serological profile three months post-treatment, suggesting potential false-positive results. The findings clearly indicate that omitting cerebrospinal fluid analysis significantly increases the risk of LNB overdiagnosis, and relying solely on neurological symptoms and serum serology leads to reduced diagnostic specificity [35].

The table below provides a structured approach to the differential diagnosis in patients with suspected neuroborreliosis, Lyme arthritis, or Lyme carditis. By presenting clinical manifestations alongside commonly considered alternative diagnoses, it may support clinicians in making more accurate diagnostic decisions in cases of nonspecific symptoms, thereby reducing the risk of both missed and overdiagnosed Lyme disease.

Table 2. Differential diagnosis of common clinical manifestations in neuroborreliosis, Lyme arthritis, and Lyme carditis.

Clinical manifestation	Clinical presentation	Differential diagnosis
Lyme carditis [36]	- Atrioventricular block - T-wave abnormalities, QT prolongation - Myocarditis or pericarditis (less common) - Rarely: new-onset heart failure, wall motion abnormalities - Clinical symptoms: fatigue, dizziness, palpitations, chest pain	- Viral myocarditis - Bacterial endocarditis - Rheumatic fever - Systemic lupus erythematosus - Syphilis
Lyme arthritis [24, 37]	- Episodic or chronic inflammation of large joints, most commonly the knees - Less frequent inflammation of small joints, the temporomandibular joint, and periarticular structures - Typically no systemic symptoms at the time of arthritis onset - Clinical presentation: swelling and moderately intense joint pain	- Septic arthritis - Gonococcal arthritis - Crystalline arthritis - Rheumatoid arthritis - Reactive arthritis - Ankylosing spondylitis - Psoriatic arthritis - Fibromyalgia - Oligoarticular juvenile idiopathic arthritis
Neuroborreliosis [30, 38]	- Garin-Bujadoux-Bannwarth syndrome - Chronic encephalitis - Chronic myelitis - Subacute encephalopathy - Memory impairment - Emotional disturbances - Polyneuropathy - Meningitis - Radiculitis and cranial neuritis - Clinical presentation: headache, neck stiffness, radicular pain, sensory disturbances, muscle weakness, memory impairment, concentration difficulties, mood disorders, sleep disturbances, chronic fatigue	- Multiple Sclerosis - Amyotrophic Lateral Sclerosis - Stroke - Peripheral facial palsy - Peripheral nervous system diseases - Migraine - Neurosyphilis - Neoplasms/tumors - Alzheimer's disease - Discopathies - Psychiatric disorders

Post-treatment Lyme disease syndrome (PTLDS)

Post-treatment Lyme disease syndrome, alongside Lyme disease itself, is increasingly being referred to as a "great imitator" due to its nonspecific symptoms—such as chronic fatigue, musculoskeletal pain, and cognitive impairment—and the high rate of overdiagnosis. Prat et al. reported that, in observational studies, misdiagnosis rates of PTLDS reached as high as 80–100%, with final, accurate diagnoses most commonly involving psychiatric, neurological, or rheumatological conditions, including disorders with prominent somatic symptoms. Contributing factors to this overdiagnosis include not only the nonspecific clinical presentation but also the use of unvalidated diagnostic tests in private laboratories and the inherent limitations of conventional serological diagnostics—such as the seronegative window in early infection, false positives, cross-reactivity, and persistent antibodies following resolved infection. Treatments administered to PTLDS patients, often prolonged and off-label, carry significant risks of adverse events, including Clostridium difficile-associated diarrhea, electrolyte imbalances, bacterial and fungal infections, sepsis, and anaphylactic reactions, particularly when administered intravenously. Prat et al. emphasize that overdiagnosis of PTLDS not only exposes patients to harmful interventions but may also delay the identification of serious underlying conditions, such as dementia or malignancy. The authors argue that, given the lack of proven treatment efficacy, diagnostic and therapeutic decisions should be made with great caution [39]. In the study by Rebman et al. (2017), it was shown that 59% of patients with clinically confirmed PTLDS received a misdiagnosis or delayed diagnosis. Due to the lack of specific biomarkers for Borrelia burgdorferi infection and PTLDS, there is a risk of both overdiagnosis and misdiagnosis resulting from the nonspecific nature of the symptoms. In searching for

significant differences between PTLDS patients and a healthy control group, reduced vibration sensation was found in 32.2% of the patients. The applied questionnaires revealed significantly higher levels of fatigue, pain, sleep disturbances, and depression, as well as lower quality of life in the PTLDS group compared to the control group ($p < 0.001$) [40].

Summary

This review provides a comprehensive analysis of Lyme disease, presenting it as one of the classic "great imitators." The study encompasses the wide spectrum of clinical manifestations that contribute to significant diagnostic challenges in both early and advanced stages of the disease. It highlights that the nonspecific nature of symptoms frequently leads to diagnostic errors, resulting in inappropriate treatment and delayed recognition of other, often serious, conditions. Particular emphasis is placed on neuroborreliosis, Lyme arthritis, and Lyme carditis in the context of differential diagnosis with other disorders. The problem of overdiagnosis of Lyme disease and post-treatment Lyme disease syndrome is also addressed, underlining the risks of unnecessary antibiotic therapy and iatrogenic complications. The evidence presented supports the necessity of applying strict clinical and laboratory criteria and conducting thorough differential diagnosis in every suspected case of Lyme disease. This work is unique, as very few review articles approach Lyme disease in a holistic manner, treating it as a condition that imitates a wide range of neurological, rheumatological, cardiac, and psychiatric disorders. Consequently, it makes an important contribution to systematizing current knowledge on differential diagnosis and emphasizes the importance of a critical interpretation of both clinical presentation and laboratory findings. The overarching conclusion is the need for high diagnostic vigilance and a careful balance between underdiagnosis and overdiagnosis of Lyme disease.

Disclosures

Author's contribution: conceptualization, KG; methodology, KP and AR; software, KG; check, KP and AR; formal analysis, AR; investigation, KP and AR; resources, AR; data curation, KG and KP; writing - rough preparation, KG; writing - review and editing, KG and KP; visualization, KG; supervision, AR; project administration, KG

Supplementary Materials: They haven't been provided.
Funding Statement: This research received no funding
Institutional Review Board Statement: Not applicable.
Informed Consent Statement: Not applicable.
Data Availability Statement: Not applicable.
Conflict of Interest: The authors declare no conflict of interest.

All authors have read and agreed with the published version of the manuscript.

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