Review

Brazilian Borreliosis: An In-depth Review of Incidence, Diagnostic Challenges, and Awareness Efforts in Brazil

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Brazilian Borreliosis: An In-Depth Review of Incidence, Diagnostic Challenges, and Awareness Efforts in Brazil

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Abstract: In Brazil, Brazilian borreliosis (BB), characterized molecularly, exhibits symptoms akin to Lyme disease (LD) but presents unique epidemiological, clinical, and morphological features. This study explores the incidence, diagnostic challenges, and awareness initiatives regarding this disease in Brazil. Employing a narrative review methodology, data were sourced from Pubmed, Ebsco, Google Scholar, and Web of Science without temporal constraints. Results reveal diagnostic complexities in Brazil due to the low sensitivity of conventional tests and the use of North American *B. burgdorferi* antigens. Despite challenges, epidemiological studies indicate an upswing in cases in humans and animals. Therefore, there is an urgent need to define new biomarkers, molecular strategies, or new antigenic targets to advance the development of vaccines and diagnostics. Early and accurate pathogen identification is crucial for active surveillance to comprehend and manage this zoonosis.

Keywords: Lyme disease; neuroborreliosis; diagnose; immunological diagnosis

1. Introduction

Lyme disease (LD) stems from spirochetes within the *Borrelia burgdorferi* species complex, a Gram-negative bacterium [1], prevalent in temperate regions like the USA, Europe, Asia, and the Middle East [2,3]. In Brazil, molecular identification of the same bacterium exists, but isolation or cultivation remains elusive [4]. Thus, the disease is termed Lyme-like or Brazilian borreliosis (BB), Brazilian Lyme-like disease (DLSB), or Baggio-Yoshinari Syndrome (BYS) in Brazil, with cases documented across various regions [5–7]. Although BB mirrors LD symptoms, notable epidemiological, clinical, and morphological differences exist [5,8].

Transmission occurs through the bite of an Ixodes tick during a blood meal, causing a multisystemic disease associated with initial phase symptoms typically including skin lesions such as erythema migrans (EM). As the disease progresses, extracutaneous manifestations may affect joints, heart, and nervous system in later stages [9–11]. Typically successful antibiotic treatment in the initial phase is typical. However, despite appropriate antibiotic therapy and an absence of clear evidence of ongoing infection, some patients present persistent symptoms. These symptoms, which include joint/muscle pain, depression, fatigue, and cognitive difficulties, are termed posttreatment Lyme disease syndrome (PTDS) or posttreatment Lyme disease syndrome-Lyme (PLSD) [12–14]. Diagnosis of this condition relies on clinical symptoms and serological tests. Nevertheless, these tests have low sensitivity and specificity in Brazil when using *B. burgdorferi* sensu stricto antigens of European or American origin. [8].

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In this review, we update information on the challenges of diagnosing LD and Brazilian borreliosis. Identifying specific target proteins as markers for disease identification and monitoring is crucial, given the lack of biomarkers hindering a deeper understanding of the condition.

2. Material and Methods

This literature review aims to provide a comprehensive overview of Lyme disease within the Brazilian context. Various search strategies were employed, encompassing Pubmed, Ebsco, Google Scholar, and Web of Science databases. Key terms such as "LD in Brazil," "Lyme pathogenesis," "Baggio-Yoshinari syndrome (BYS)," "Persistence of Lyme disease," "Borreliosis and diagnosis," "spirochete," and "tickborne disease" were utilized. The search was not constrained by a specific timeframe, ensuring coverage of studies over an extended period. Additionally, animal and in vitro studies were included in the examination. Titles and abstracts were meticulously evaluated during screening to identify pertinent works.

3. Results

3.1. History of Lyme Disease and Brazilian Borreliosis

In the historical context of LD, Alfred Buchwald's 1883 clinical descriptions marked the inception, detailing dermatological manifestations now recognized as chronic atrophic acrodermatitis (ACA) [15]. Benjamin Lipschutz and Arvid Afzelius, early in the 20th century, associated *Erythema migrans* with tick bites, with Afzelius providing specifics in 1910 [15]. However, it was only in 1976 that LD was officially identified in Lyme, Connecticut, USA, by Dr. Allen C. Steere [16]. The significant milestone of isolating the etiological agent *Borrelia burgdorferi* occurred in 1982, credited to Willy Burgdorfer [17].

While LD is a prevalent zoonosis in the USA, borreliosis has been documented in South American countries, including Argentina, Bolivia, Colombia, Venezuela, Chile, and Brazil [18]. In the 1980s, the first cutaneous manifestations were diagnosed in Manaus, followed by cases in the 90s with tick bites and seropositivity in Rio de Janeiro and São Paulo states [19,20]. Secondary manifestations like Lyme meningitis were reported in Mato Grosso do Sul staite 1996 [21]. Subsequent studies highlighted recurrent symptoms posttreatment, deviating from patterns observed in American and European Lyme Borreliosis (LBP) [22].

3.2. Morphological Features of Borrelia

Belonging to the order Spirochaetales, Borrelias consists of 42 species categorized into two main groups: the relapsing fever group (GFR) and the *Borrelia burgdorferi* sensu lato (Bbsl) group [23]. Of the Bbsl group, 20 species are associated with Lyme Borreliosis (BL) [23]. Spirochetes exhibit an elongated, corkscrew-like structure with axial filaments and reproduce through transverse binary fission [24,25]. Notably, Borrelia lacks lipopolysaccharides (LPS) in its outer membrane but possesses a lipid bilayer composed of phospholipids, glycolipids, and lipoproteins [16,26] (Figure 1). The Bbsl complex has a conserved linear chromosome but displays high variability in its 21 plasmids, potentially influencing clinical manifestations and distribution [27].

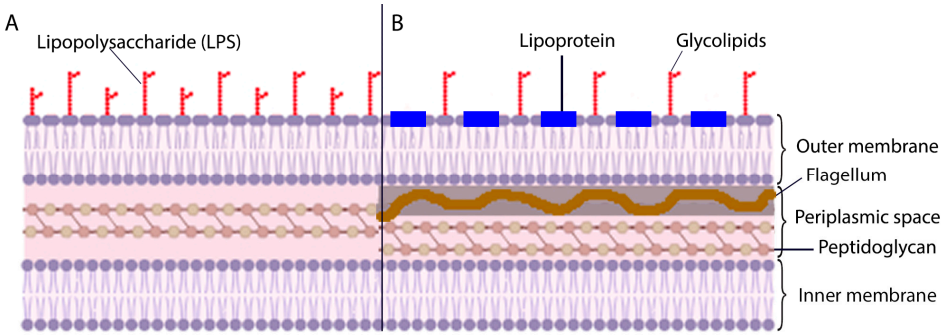

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Figure 1. Representation of the membrane structure. (A) Gram-negative bacterial membrane. (B) Spirochete membrane. The outer membrane of spirochetes has several lipoproteins and glycolipids that do not include LPS.

The spirochete adapted to the Brazilian environment exhibits an "L" shape, suggesting a cell wall deficiency that may enable intracellular localization. PCR tests for flaA, flab, and Osp A genes yielded negative results, but Western Blot analysis consistently identified the 41 kD band. The flgE gene, responsible for the flagellar hook protein, was later confirmed, hinting at an evolutionary process that reduced immunogenicity and antibody production, potentially contributing to survival and dissemination in the Brazilian environment [4,8,22,28].

3.3. Pathogenesis

Although *B. burgdorferi* does not produce LPS, OspA and OspB proteins play pivotal roles in tick intestine survival [29]. The transition from tick intestine to salivary glands involves a shift in protein expression, with decreased OspA and increased OspC facilitating host infection [30]. Borrelia infection initiates when the organism enters the host, spreads to various tissues, and causes diverse manifestations, including neuroborreliosis [27].

Borrelia relies on its outer membrane lipoproteins and adhesins to establish virulence and adhere to host tissues. These proteins activate immune responses and interact with target tissues. Despite immune system activation, Borrelia often persists, maintaining infection [29]. Macrophages internalize Borrelia through opsonization, a process recognized by receptors such as FcγR and CR3. Notably, the absence of FcγRIIb function may broaden B cell activation and lead to autoimmune responses [31,32]. Neutrophils and macrophages, activated by Toll-like receptors (TLRs) and NOD-like receptors (NLRs), recognize Borrelia peptidoglycan, inducing pro-inflammatory responses [33]. As observed in BB patients, pro-inflammatory cytokines like IL-6, IL-12, TNF-α, and pro-IL1β are activated [34,35]. During infection, elevated levels of IL-8, MIP-1/CCL3, MIP3B/CCL19, and IL-17A were identified, particularly during the acute phase of the disease [36]. These findings indicate a comprehensive immune response, including the Th2 response, which stimulates interleucin-4 (IL-4) production. Interestingly, Borrelia's "L" form potentially evades Th2 response [37].

3.4. Current Situation of Lyme Disease in Brazil

3.4.1. Tick Biological Cycle and Its Relationship with the Spread of the Disease

Tickborne diseases, such as those caused by the bacteria *B. burgdorferi*, have emerged as a significant epidemiological problem in various regions worldwide, particularly in countries with tropical and subtropical climates where ticks are more prevalent [38]. Ticks from the Argasidae and Ixodidae families (Figure 2) are crucial in transmitting *Borrelia spp. Ixodes spp*. is a major transmitter in Europe, Asia, and North America [14,39].

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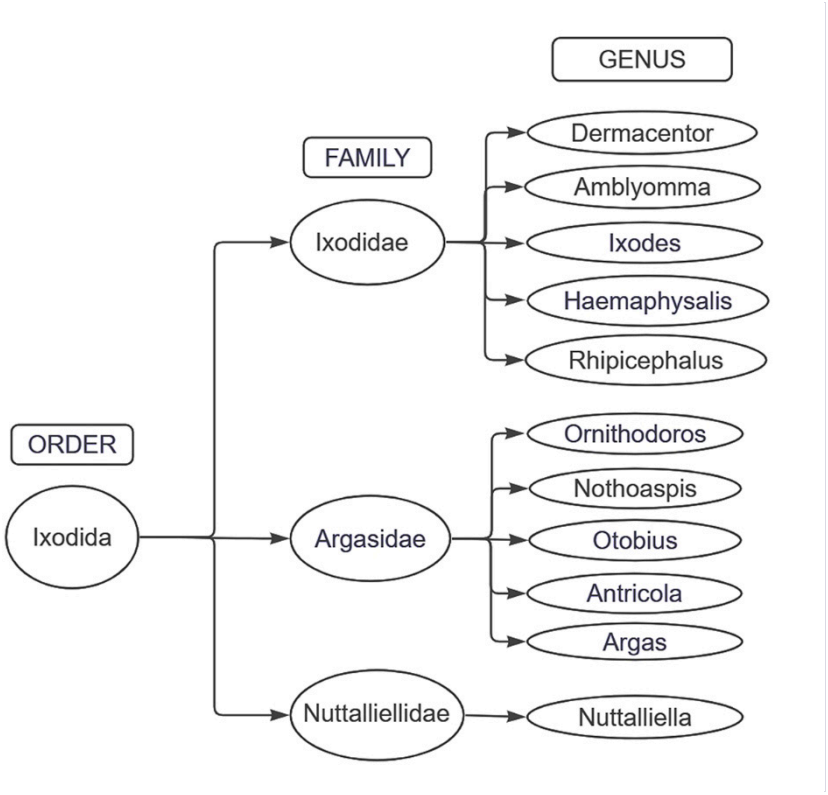

Figure 2. Taxonomic classification of the Ixodida tick species.

Brazil's diverse ecosystem and climatic conditions create a conducive environment for ticks. The predominant tick species, acting as disease vectors, belong to the Ixodidae and Argasidae families [38] (Figure 2). Molecular and serological studies in Brazil have identified both Ixodes and Amblyomma ticks participating in the transmission, with ticks becoming infected through feeding on vertebrate reservoirs carrying bacteria [40–42]. Transmission routes include transovarial, where inefficiency in maintaining *B. burgdorferi* has been reported, and the transstadial route, where spirochetes migrate to the tick's salivary glands during feeding and subsequently inoculating the vertebrate host's skin [43,44]. While deer and rodents are the primary reservoirs, domestic animals like dogs and horses can also play a crucial role [4,45]. Humans become accidental hosts when bitten by infected ticks, especially the challenging-to-detect nymphs [45].

3.4.2. Clinical Picture of DLSB/Lyme

Lyme disease exhibits a range of clinical manifestations, posing challenges for accurate diagnosis. Symptoms like fever, fatigue, headache, muscle and joint pain, and the characteristic skin rash erythema migrans (EM) can resemble other medical conditions. Notably, not all patients exhibit the skin rash, complicating early diagnosis. Studies suggest asymptomatic cases in Europe and a subset in the USA [1,46].

LD progresses through three stages: Acute infection, disseminated disease with neurological or cardiac involvement, and Chronic infection marked by arthritis (Table 1). The absence of specific symptoms in all patients complicates diagnosis. Apart from initial symptoms, Lyme disease can lead to systemic manifestations like eye problems, joint pain, and neurological and cardiac symptoms weeks or months post-infection, potentially resulting in late diagnoses and complications [47]. Neurological diseases associated with Lyme carditis, while rare, can lead to serious complications such as atrioventricular heart block and sudden death if untreated [46,48,49].

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Table 1. Clinical manifestation of Brazilian borreliosis (Lyme disease).

Stage of the disease	USA	Brazil	Ref.
Acute infection	ME, fever, headache, arthralgia, myalgia.	Cutaneous manifestation, fever, general malaise, myalgias	[4,8,46,47]
Disseminated Disease	Migratory arthralgias, Lyme carditis, meningitis, facial paralysis		
Chronic infection	Encephalopathy, monoarthritis, peripheral neuropathy	Neurological changes, ocular symptoms, psychiatric and psychosocial disorders, oligoarthritis, autoimmune symptoms, and chronic fatigue syndrome	

[1] EM, erythema migrans.

Furthermore, studies have identified morphological, epidemiological, and laboratory differences between Brazilian Borreliosis (BB) and North American Lyme disease, influencing clinical manifestations in Brazil [22–45]. Prolonged clinical evolution and recurrent symptoms after treatment are observed, with peculiarities including chronic fatigue syndrome and autoimmune/allergic diseases [50–56]. Clinical manifestations of BB are categorized into initial and late stages, reflecting the flu-like symptoms and more severe symptoms, respectively [4,8,36,53,56].

3.4.3. Epidemiological Trends of Brazilian Borreliosis Disease

Lyme disease was first reported in the United States in 1991 [57], and from 1996 to 2023, the CDC reported 761.143 cases, with notable peaks in 2009, 2017, and 2022 (Figure 3). However, the case definition for Lyme disease has changed over the years, and these changes may influence surveillance data.

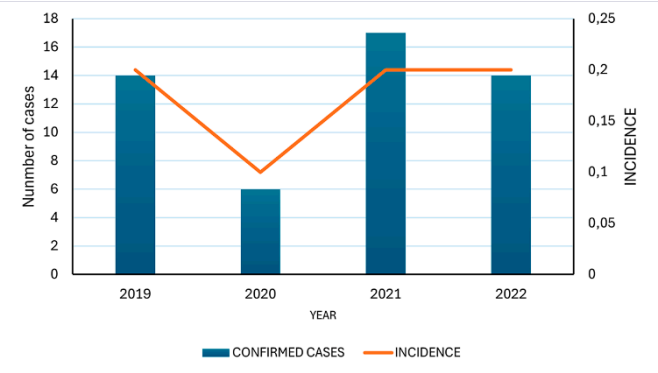

Figure 3. Number of reported cases of Lyme disease in the United States of America, 1996-2022.

Figure 3 shows the number of cases considering the changes in force in 1996, 2008, and 2022. Despite DLSB being considered rare in Brazil, seropositivity rates in animals, particularly dogs and horses, suggest a potential risk of transmission [58–64]. Cases of DLSB in Brazil were identified three decades ago [65], with some states instituting notifications. Notably, there was a surge in reported cases in specific regions, emphasizing the need for active surveillance and accurate diagnoses [66–69].

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In Santa Catarina, 20.4% of reported cases and an incidence of 0.7 cases/100 thousand inhabitants were laboratory-confirmed as Lyme Disease, a notable proportion considered autochthonous [70] (Figure 4). These findings underscore the urgency for enhanced surveillance and precise diagnostics to comprehensively understand the disease's spread and incidence.

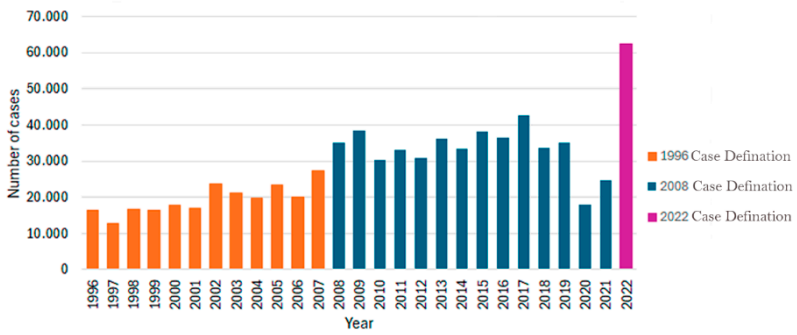

Figure 4. The number of confirmed cases of Lyme Disease in Santa Catarina state, Brazil (2019 to 2022) was reported by the Santa Catarina Epidemiological Surveillance Directorate.

3.5. Challenges in Brazilian Lyme-like Disease Diagnosis

In Brazil, diagnosing and recognizing Lyme disease remains challenging due to the diversity of tick species and bacterial strains and variations in clinical and epidemiological aspects compared to North America [52]and Europe [15]. Difficulty in serological diagnosis, cross-reactions, and limitations of available tests add to the complexity [53,54].

Availability of Tests and Their Limitations in the Brazilian Context

Effective treatment and prevention of long-term complications in Brazilian Lyme-like disease hinge on accurate diagnosis [9,71,72]. Over the past decade, diagnostic accuracy has become challenging due to diverse clinical presentations and test limitations. Serological tests like ELISA and Western blot are commonly used [52], but false-positive and false-negative results compromise reliability [4,22,73]. While sensitive, PCR and other molecular techniques face challenges in diagnosing persistent arthritis [74]. Various diagnostic methods, including histopathology and imaging, have been explored, each with limitations [75–78].

In Brazil, the adoption of ELISA and WB tests has been hindered by diagnostic inaccuracies related to antigen variety and test criteria [4,22,56]. Newer methods like the Modified Two-Stage (MTTT) method promise to improve diagnostic accuracy, but challenges persist [79–82]. The intricacies of Brazilian *B. burgdorferi*, such as pleomorphic morphology, temperature sensitivity, and slow growth cycle, pose obstacles to effective diagnosis [4,36].

The challenges in diagnosing BB include the similarity of initial symptoms to other diseases, limitations in serology, the impossibility of pathogen culture and isolation, and the necessity of excluding other conditions presenting similar symptoms[83–85]. Comprehensive and specific diagnostic approaches are crucial for BB, highlighting the need for ongoing research to enhance understanding and management.

3.6. Characteristics of the Antibody Response to B. burgdorferi

The dermal inflammatory process, triggered by tick bites, leads to *Erythema migrans* [86]. Antibody production follows, starting with IgM, and is detectable from the third to fourth-week post-infection. IgM levels peak between the sixth and eighth week, indicating a recent infection [87–90]. However, the persistence of IgM responses for years [88,91] and IgG poses challenges in distinguishing between active and inactive infections [82]. Moreover, IgM antibodies may have the potential to cross-react with antigens that are unrelated to Borrelia [92,93]. During the acute phase, IgA is produced, particularly in the cerebrospinal fluid [94–96]. In addition to these antibodies, the generation and persistence of IgE antibodies have been observed in children [97]. This observation

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suggests using both IgA and IgE as diagnostic markers. Further research is needed to understand the role of IgA and IgE in *B. burgdorferi* infection and its implications for diagnosis and treatment.

3.7. Recent Advances in DL

Despite the availability of diagnostic tests, challenges persist, and new technologies are emerging. Digital PCR (dPCR) is gaining popularity due to its accuracy and sensitivity, especially in cerebrospinal fluid samples[98,99]. Challenges related to Posttreatment Lyme Disease Syndrome (PTLDS) prompt exploration of biomarkers [100] and antigens using artificial intelligence (AI) and machine learning [101,102]. Among these, elevated levels of CCL-19 [103] and apolipoprotein B [104] have been observed in PTLDS patients, which could serve as biomarkers. Petzke et al. identified 20 genes capable of discriminating with high accuracy (97%) between individuals with acute disseminated Lyme disease and healthy controls and between those in the acute phase and recovery [105]. Additionally, regarding metabolomic biomarkers, sialic acid in N-glycans plays a significant role in many biological activities and in diagnosing Lyme disease [106]. These technologies will contribute to identifying new biomarkers, differentiating between Lyme disease and other infections, and enhancing understanding for better diagnosis and treatment for tickborne disease and other infectious diseases [106].

4. Conclusions

The genetic and morphological variability of this bacterium and the disease's unique clinical manifestations pose challenges to the precision of conventional diagnostic methods. Epidemiological studies highlighting a surge in cases across various country regions underscore the urgency of enhanced surveillance and precise diagnostic procedures. Consequently, the constrained availability of sensitive and specific tests and the absence of standardization present a formidable challenge in identifying and monitoring this disease within the Brazilian context.

In this context, novel approaches, including exploring specific and critical epitope biomarkers and developing more refined diagnostic methods tailored to the nuances of Brazilian Borreliosis, become indispensable for achieving early and accurate diagnoses. Such advancements could enhance the quality of life for individuals impacted by this condition. Recognizing the intricacies of diagnostics and the continual need for methodological refinement is pivotal in advancing the comprehension and management of this disease in Brazil.

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