LYME DISEASE: DIAGNOSTIC CHALLENGES AND MISDIAGNOSIS RISKS

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ABSTRACT

Lyme disease (LD), a tick-borne illness caused by Borrelia burgdorferi, presents significant diagnostic challenges due to its variable and often non-specific symptoms, which mimic other conditions. This research investigates the difficulties in diagnosing LD, explores how healthcare professionals can improve the diagnostic accuracy, and identifies key factors influencing correct diagnosis.

The study analyzes existing literature and medical texts and incorporates insights from a specialist interview. B. burgdorferi's antigenic variability, the low prevalence of the pathognomonic erythema migrans rash, and the limitations of current two-tiered serological testing contribute to diagnostic uncertainty. This research highlights the importance of a thorough patient history, physical examination, and awareness of LD's diverse clinical presentations. It also addresses the challenges posed by varying laboratory criteria for test interpretation, which can potentially lead to false negatives.

This study emphasizes the need for enhanced clinician education and standardized diagnostic protocols to improve early LD detection and ultimately patient outcomes.

The relevance of this research is to highlight the complex interplay of factors contributing to misdiagnosis or delayed treatment of LD. By examining the limitations of current diagnostic methods and emphasizing the crucial role of thorough clinical assessment and a high index of suspicion, this study reinforces the critical need for improved clinician education and standardized diagnostic protocols. Addressing these challenges will ultimately lead to earlier and more accurate diagnoses, improving patient outcomes and mitigating the long-term consequences of untreated LD.

INTRODUCTION

This article explores the diagnostic challenges of Lyme disease (LD), common misdiagnoses, necessary laboratory tests, and key clinical signs and symptoms. This investigation will try to answer the following questions: Why is it so difficult to diagnose Lyme disease when the first signs and symptoms appear? How can the health working population be better prepared to make this diagnosis? What are the factors that determine whether the correct diagnosis for this disease is made?

Lyme disease, or borreliosis, is caused by the bacterium *Borrelia burgdorferi* and is transmitted to humans through the bite of an infected Ixodes scapularis, also known as the blacklegged tick or as the deer tick. It is the most common tickborne infectious disease in the United States.

Tickborne refers to the way of transmission, the only way to get the disease is by the bite of an infected tick (NIAID, 2024).

The definition of diagnosis is the process of identifying a disease, condition, or injury from its signs and symptoms. A health history, physical exam, and tests, such as blood tests, imaging tests, and biopsies, may be used to help make a diagnosis (NIH).

B. burgdorferi is a gram-negative spirochete tick-borne bacterium, and it has a wide genetic variability. The only significant variation among species of Borrelia is concerning their antigenic structure. The antibodies first produced act as a selective factor that allows the survival only of distinct antigenic variants. The recurrence course of the disease seems to be caused by the multiplication of such antigenic variants, against which the host must develop new antibodies. Definitive recovery is associated with the presence of antibodies against several antigenic variants (Morse et al. 2019).

The pathogenic process of *B. burgdorferi* is a result of an inflammation process, liberation of cytokines, dissemination, and adherence of the microorganism to different tissues (Almodóvar, 1997).

In the United States, the age distribution of LD is typically bimodal, with peaks among children between 5 and 15 years of age and adults between 45 and 55 years of age. The incidence is higher among men than among women in those <60 years of age. In the northeastern United States and most of Europe, the peak months of disease are June and July, which is owing to the feeding habits of nymphal ticks. In Mexico, 398 human cases for Borrelia-infection were recorded between 1939 and 2020 (Steere et al., 2016) (Colunga-Salas et al., 2020).

Through an approach based on the analysis of literature reviews, medical books, and an interview with the specialist Dr. Raphael Stricker, it is hoped to provide a practical understanding of the difficulties of diagnosing LD, how can doctors be better prepared to make a successful diagnosis of the disease and the factors that determine a correct diagnosis for LD.

DISCUSSION

History.

In December 1975, Steere and Malawista led a surveillance study to investigate the cause of a sudden outbreak of rheumatoid arthritis in and around Lyme, Connecticut. The study focused on three contiguous towns where 51 residents were diagnosed with juvenile arthritis; the investigation consisted of thorough physical examinations and blood work of each patient on site at Yale University. Approximately 25 percent of the patients in the study reported skin lesions for four or more weeks preceding the onset of arthritis symptoms. As early as 1976, Steere and Malawista suggested the tick as the vector of "Lyme arthritis", and in 1978 they showed epidemiological evidence for a tick vector. In 1983, Burgdorfer and colleagues isolated the infectious agent that causes LD (Elbaum-Garfinkle, 2011).

Epidemiology.

LD is the most common vector-born disease in both Europe and North America; more than 400,000 cases have been reported in the United States since 2004. Although the disease was named in the mid-1970s, typical cases were described in Europe as early as 1883. (Mead, 2022) The epidemiology of LD is complex, and a detailed understanding can be challenging for busy clinicians, yet some epidemiologic knowledge is clinically useful. Presenting symptoms of LD can be nonspecific, and a patient's exposure history strongly influences the prior probability of disease (Mead, 2022).

Pathogeny.

The genus *Borrelia* is a member of the family *Spirochaetacaea*, which are gram-negative bacteria characterized by a wavelike body and flagella (Elbaum-Garfinkle, 2011).

B. burgdorferi stimulates various inflammatory cytokines like IL-1, IL-6, and TNF-α, that could play some role in the inflammatory reaction that accompanies the disease. The dissemination of the microorganism is facilitated by the high permeability of blood vessels and the active penetration of the bacterium through the endothelial membranes. The invasion of different tissues is the result of the adherence of the bacterium to different cell types, including fibroblasts and endothelial cells. The immune response to *B. burgdorferi* is not effective in eradicating the bacteria and may contribute to the disease by developing an autoreactive process. This reaction is based on antigenic cross-reactivity between epitopes common to the agent and the host, especially those located in the so-called "heat shock or stress proteins" of which 5 to 7 have been detected in B. burgdorferi (Almodóvar, 1997).

Signs and symptoms.

As mentioned before, LD is caused by Borrelia burgdorferi sensu lato, is a multi-organ infection with dermatological, rheumatological, neurological and cardiac manifestations. The main characteristic is a skin lesion, the infamous erythema migrans or colloquially known as the bulls-eye rash (Wilske et al., 2007).

During the interview with Dr. Raphael Stricker, a question was answered about the famous bulls-eye rash, where he answered that the erythema migrans only shows on about 10% of the patients infected by *B. burgdorferi*, some may think that the rash always appears on patients, although it is a pathognomonic sign, it does not always appear, which is also one of the factors that doctors dismiss while trying to make the diagnosis since some think that if the patient has no history of a rash, the disease is not there, which in some cases may be true, but not in the majority; which is why it is important not to dismiss the possibility of LD even if the patient did not present the characteristic erythema migrans.

LD presents differently in every patient, there are many symptoms a patient can develop depending on the system most affected; there are neurological symptoms, cardiovascular symptoms, and the most seen are the musculoskeletal symptoms. The main symptoms include fatigue, myalgias,

arthralgias, "brain fog", headaches, malaise, sometimes fever can appear, and regional lymphadenopathy (Stricker, 2024) (Steere et al., 2016).

In some cases, there are neurological symptoms, like neuropathic pains, loss of sensibility, and trigeminal neuropathy, and sometimes both PNS and CNS abnormalities, although the last two are rare, they can happen. (Stricker, 2024) Acute cardiac involvement can occur during early disseminated infection and mostly manifests as fluctuating degrees of atrioventricular nodal block; other, less common, manifestations include acute myopericarditis or mild left ventricular dysfunction and, rarely, cardiomegaly or pancarditis (Steere et al., 2016).

Regarding the chronic type of LD, patients can present post-Lyme syndrome (PLS), which is explained by the presence of chronic inflammation. All this attributable to the persistence of the bacteria despite a proper treatment. Prolonged symptoms can lead to considerable suffering of patients, some of the symptoms in chronic LD include fatigue, depression, anxiety, memory and concentration problems, pain and body aches, and sleep problems (Lacout, 2018).

The importance of diagnosing LD on time, and patients receiving the proper treatment plan, is important to try to avoid chronic LD or PLS, which are very difficult to treat and are even more difficult for patients to manage.

The basis to a diagnosis.

There are 3 stages of infection by B. burgdorferi: early localized, early disseminated, and late disseminated. The classic sign of localized infection is the erythema migrans, or bulls-eye rash; accompanying signs and symptoms might include fever, lymphadenopathy, myalgias, or arthralgias. When untreated, the infection can develop into a disseminated infection, where it can cause neurological symptoms, cardiovascular symptoms, and persistent musculoskeletal symptoms (Moore et al., 2016) (Stricker, 2024).

The recommended approach for laboratory diagnosis of LD is a 2-tiered serologic test comprised of ELISA, followed by a reflex Western immunoblot. (Moore et al., 2016) A first test is done with enzyme immunoassay or immunofluorescence assay, if the test is positive or throws an equivocal result, with signs and symptoms present for 30 days or less, the secondary test recommended is an IgM and IgG Western blot; when the signs and symptoms are present for more than 30 days, the second test recommended is only an IgG Western blot. This 2-tiered serologic analysis has a sensitivity of approximately 70-100% and a specificity >95% for disseminated LD. A positive IgM Western blot is indicated by the scored presence of ≥2 of 3 bands, and a positive IgG result is indicated by the scored presence of ≥5 of 10 bands (Moore et al., 2016).

When asking Dr Stricker about the laboratory blood tests done to diagnose LD, he mentioned that sometimes tests can give false negatives because of the lack of bands required by the test to be positive, this depending on the

laboratory where the test is being processed, he mentioned that some laboratories have different criteria of positive bands required to mark a positive LD test, causing some patients to have false negative results and if/when getting the test realized in a more specialized laboratory, it will be more accurate to get the right result. He also mentioned how sometimes the test for B. burgdorferi can be negative, but while testing for coinfections, and these coming out as positive, we can automatically say that there is also an infection by B. burgdorferi. Some of the difficulties of analyzing the laboratory tests come from not having enough clarity on the testing process and the different criteria that a sample must meet to interpret a test as positive or negative (Stricker, 2024).

As mentioned before, different laboratories have different criteria when marking serological tests as positive or negative; for example, in IGeneX laboratories, the interpretation for a positive IgG ImmunoBlot test consists of two or more of the following bands being present: 23, 31, 34, 39, 41, and 93 kDa; a positive IgM test consists of two or more of the following band being present: 23, 31, 34, 29 and 41kDa; while according to CDC regulations and NYS criteria, which are the ones that other laboratories follow, the criteria for both a positive IgG and IgM test consists of 5 bands out of 10 being present, thus making it very possible to patients to receive a false negative result and presenting LD symptoms, thus making it more difficult to get a correct diagnosis.

Misdiagnosing LD.

The symptoms of LD are similar to a variety of autoimmune musculoskeletal diseases, like rheumatoid arthritis, lupus, dermatomyositis, Guillain-Barre syndrome, among other diseases like fibromyalgia. LD symptoms may be like other medical conditions, making diagnosing a challenge, which is why it has been coined "the great imitator" along with syphilis. Some patients with LD have been misdiagnosed with multiple sclerosis, fibromyalgia, chronic fatigue syndrome, autoimmune diseases including lupus and RA, polymyalgia rheumatica, and thyroid disease, among others (Cameron, 2021).

Which is why a proper patient history, patient physical examination, and specific laboratory testing are required to achieve a correct diagnosis; also having the necessary knowledge about LD to think of it as a possibility (Stricker, 2024).

Treatment.

According to the guidelines of the IDSA, recommended antibiotic treatment for LD includes doxycycline or amoxicillin, which are generally effective on the early stages of LD. Second choice treatment includes amoxicillin, cefuroxime axetil or erythromycin. Treatment duration varies depending on the stage and severity of infection. Intravenous regimens are indicated in case of severe cardiac or nervous system involvement. Post-Lyme-disease syndrome (PLDS) is characterized by symptoms such as fatigue, myalgia, arthralgia or dysthesia/paresthesia. Long term antibiotic

regimens are targeted to eliminate spirochetes that might survive in areas less accessible to the immune system (Bratton et al., 2008)(Seidel et al., 2007).

There are different regimens to choose from to treat LD, depending also on coinfections, symptoms, and how the patient responds to the treatment, sometimes it is necessary to combine certain antibiotics to be able to reach the spirochete and treat the infection. Treatment can be difficult depending also on the stage of the infection and the severity of the symptoms (Stricker, 2024).

LD is not like other common diseases, it requires a prolonged treatment regimen, which has caused a controversy among physicians around the world. Opinions vary among different physicians and specialists, but it has been proved that prolonged treatment is the best way to go in treating LD. The divergence in opinion creates a significant divide within the medical community, leaving patients to navigate conflicting recommendations and often facing challenges in accessing and affording prolonged treatment. This ongoing debate highlights the need for further research to achieve a correct treatment plan and to teach other physicians on the type of antibiotic regimen for treating LD patients.

METHODOLOGY

Design of the investigation.

The design of this research work, where the goal was to acknowledge the difficulties in diagnosis of LD, the proper process to a correct diagnosis of the disease and the reasons why it can be misdiagnosed; a data collection was carried out through the review of several published literatures on the subject and an interview with the specialist Dr. Raphael Stricker.

Focus of the investigation.

The focus of this research work is documentary, based on the recompilation and analysis of literature about LD, how it is diagnosed, and the different contributing factors to a successful diagnosis. No surveys or direct observations were conducted, but rather the focus was on reviewing academic articles, literature about the disease, books, and an interview with an expert. It is based on secondary sources, and the synthesis and analysis of existing information.

Applied technic.

The technique applied in this research is the bibliographic review, which includes the recollection, evaluation, and synthesis of information from secondary sources that were considered relevant. This writing focused on an exhaustive analysis of literature and existing information that could answer the research questions: Why is it so difficult to diagnose Lyme disease when the first signs and symptoms appear? How can the health working population be better prepared to make this diagnosis? What are the factors that determine whether the correct diagnosis for this disease is made?

CONCLUSIONS

Diagnosing Lyme disease remains a complex challenge. The variability of symptoms, the infrequent presentation of the characteristic rash, and the limitations of current diagnostic tests all contribute to the difficulty. Improving diagnostic accuracy requires a multifaceted approach. Firstly, clinicians must be educated about the broad spectrum of LD and its manifestations and be aware that the absence of an erythema migrans does not rule out LD as a possibility.

Secondly, standardized protocols for patient history taking and patient examination are crucial, emphasizing the importance of considering LD in the differential diagnosis, especially in endemic areas. Thirdly, a deeper understanding of the complexities of the serological testing, including the potential for false negatives due to varying laboratory criteria, is essential. Ultimately, improved clinician awareness, standardized diagnostic practices, and more reliable testing will lead to earlier and more accurate diagnoses, improving treatment outcomes and reducing the burden of this challenging disease.

Lastly, improving medical education and standardized protocols play a crucial role in early LD detections. A better education would empower clinicians to recognize LD manifestations, even without the characteristic erythema migrans rash. A proper education about the symptoms of LD, the epidemiology of the disease, and proper diagnosing methods, could improve the timely detection of LD. Standardized protocols would ensure systematic evaluation of suspected LD patients, having clear protocols for history taking, physical examination, and test interpretation would enable earlier and more accurate LD identification, improving treatment outcomes and reducing the disease burden.

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