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Diagnosis, Clinical Manifestations and Treatment of Lyme Disease

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Abstract

Introduction and purpose

Lyme disease was identified in the 1970s. It is an anthrozoosis caused by spirochetes from the *Borrelia* family. This disease is the most common one caused by pathogens transmitted by ticks. It can manifest in various ways and typically progresses through three phases, each of which can present characteristic symptoms of infection. However, it often progresses asymptotically. Antibiotics are widely used in the treatment of various forms of Lyme disease and demonstrate satisfactory efficacy. However, the most important aspect is the prevention of infections through personal protection against exposure. The aim of the article is to summarize information on Lyme disease, its risk factors, diagnosis, clinical manifestations, and treatment.

Materials and methods

The literature available in the PubMed database is searched using terms such as Lyme borreliosis and Lyme disease.

Results

Lyme disease is a moderately understood condition. Its risk factors have been studied, allowing us to identify those particularly at risk. However, despite this, the condition often presents diagnostic challenges, requiring considerable experience from clinicians. The disease can manifest in various ways, and antibiotics are an effective therapy in most cases. Despite numerous scientific studies on Lyme disease, not all pathophysiological mechanisms have been elucidated. Additionally, there is an ongoing debate regarding the validity of post-treatment Lyme disease syndrome (PTLDS).

Conclusions

Research on Lyme disease continues to provide new information, from diagnostics and clinical manifestations to treatment. Knowledge about infections caused by genospecies of the *Borrelia* family is extensive. However, there are still areas that are less well understood.

Keywords

Lyme borreliosis, Lyme disease, Lyme disease diagnosis, Lyme disease clinical manifestations, Lyme disease treatment

1. Introduction

Lyme borreliosis, also known as Lyme disease is the most common illness caused by tick-borne pathogens. [1] This disease can affect various systems, such as the skin, musculoskeletal system, cardiovascular system and nervous system. Diagnostic challenges associated with this condition arise from the diversity of symptoms that manifest in the early stages of the disease, prior to the development of a serologic response. [2,3] On the other hand, some patients may not exhibit symptoms but still seroconvert and develop the disease. [4] Currently, no vaccines are available for humans, and treatment is sometimes ineffective. Therefore, an important aspect is the utilization of measures aimed at reducing contact with ticks. [5]

2. Objective of the work

The aim of the study is to describe the risk factors, diagnosis, clinical manifestations and the treatment of Lyme borreliosis.

3. Description of the state of knowledge

Lyme borreliosis

The disease was identified in the 1970s. [6] Lyme borreliosis is an anthrozoosis illness caused by spirochetes from the *Borrelia* family. [2,3] In Europe, genospecies such as *Borrelia afzelii*, *Borrelia burgdorferi sensu stricto*, *Borrelia valaisiana*, *Borrelia garinii*, *Borrelia lusitaniae*, *Borrelia bavariensis*, *Borrelia bissetii* and *Borrelia spielmanii* have been identified. [4] The bacteria are transmitted by ticks- in Europe, mainly by species *Ixodes ricinus* and *Ixodes persulcatus*. [2,3,4]

Epidemiology

Lyme disease is the most commonly diagnosed tick-borne illness. In Europe, approximately 65,000 people experience symptoms related to the infection, while in the United States, as many as 300,000 individuals are affected annually. [1] It is assumed that in Poland the incidence is 20-40/100000 PPY. [7] A significant proportion of infections, however, proceed asymptotically - approximately 50% in Europe. [4] The manifestation of symptoms is similar in adults and children. [6]

Pathogenesis of infection

Transmission of Lyme disease occurs through the bite of a tick infected with the bacterium *Borrelia burgdorferi*. When an infected tick bites a human, the bacteria can be transferred into the human body, leading to infection. [1] For bacterial transmission from a tick to occur, approximately 36 to 48 hours of contact are required. In most cases, infection is transmitted by immature ticks, which, due to their lack of engorgement, are more difficult to detect by the human eye. [8] The initial serological response involves the production of immunoglobulin M antibodies (IgM), which become detectable within several days to a few weeks after the onset of infection. Subsequently, immunoglobulin G antibodies (IgG) appear, detectable approximately 1-2 months post-infection. These aforementioned classes of immunoglobulins persist in the body for up to 10-20 years following the onset of infection. [4] Additionally, as a result of a strong inflammatory response in the infected tissue area, two metabolic pathways are stimulated. The first is the lipoxygenase pathway (LOX), which generates leukotrienes (LT), lipoxins (LX), and hydroxyeicosatetraenoic acid (HETE). The second is the cyclooxygenase pathway (COX-1 and COX-2), which produces prostaglandins (PG) and thromboxane (TX). [9]

Stages of infection

Lyme disease progresses through three stages, each with its characteristic symptoms. The first stage of infection is localized and presents as erythema migrans (EM). The subsequent stage of untreated infection is early disseminated disease, which manifests as neuroborreliosis

(LNB) and myocarditis. The final stage is late disseminated disease, which includes Lyme arthritis. [6]

4. Medical literature review

Risk factors

The highest risk of infection occurs between March and November, when there is the highest tick activity.[1] Exposure to infected Ixodes ticks appears to predominantly occur in the household environment and the nearest vicinity. I. R. Fischhoff et al. conducted a meta-analysis assessing where the highest number of tick bites occur – in the yard, immediate neighborhood, and public spaces The analysis revealed that the greatest risk of infection is in the immediate neighborhood vicinity of the residence. This is due to human mobility, which increases exposure to tick bites while moving.[10] Among the professions particularly susceptible to tick bites and consequently contracting Lyme disease are forestry workers, military personnel stationed in wooded areas, and veterinarians.[1]. Additionally, outdoor recreational activities contribute to increased exposure and raise the risk of infection. [4].

Diagnosis

Diagnosis relies on the presence of specific clinical symptoms in the patient and performing serological tests- which are particularly useful when the symptoms of the disease are nonspecific. [11] The serologic testing protocol comprises two phases, enhancing both specificity and sensitivity. The first step is to perform an enzyme-linked immunosorbent assay like ELISA, which is used to detect the presence of specific IgG or IgM antibodies. Confirmation entails obtaining two positive samples in the first phase, which necessitates a subsequent stage involving Western blot analysis. This procedure also identifies specific antibodies. [4] Patients who obtained positive results in both stages of the examination will be diagnosed with Lyme borreliosis. However, individuals with a positive result in the first stage and a negative result in the second stage will not be treated- they will instead be referred for further monitoring. In clinical practice, diagnosing based on the interpretation of serological tests is complicated. Non-infected individuals may receive a positive result due to the presence of immune antibodies. On the other hand meta-analysis conducted by M. M. G. Leeflang et al. showed that some of infected individuals may have a negative result if their immune response is delayed. [11]. This publication demonstrate that Lyme disease is often overdiagnosed, especially when the patient presents with nonspecific symptoms of the disease. [12] Research indicates that a new perspective on diagnostic markers for Lyme borrelia may be prostaglandins. The levels of these substances are significantly elevated in patients infected with Borrelia causing Lyme disease compared to the control group consisting of healthy individuals. [9]

Clinical manifestations

Lyme disease can manifest in various ways. Early-stage symptoms mostly include erythema migrans, accompanied by fever and chills. Another early skin manifestation is borrelial lymphocytoma. [13] In the subsequent stage, characteristic symptoms of the nervous, musculoskeletal, and cutaneous systems appear. The ultimate complications of untreated Lyme disease include arthritis, neuroborreliosis, and myocarditis. [9] In some patients, after

treatment, Post Treatment Lyme Disease Syndrome (PTLDS) may occur, affecting about 10% of patients. PTLDS symptoms include diffuse pain, cognitive problems, and weakness. [12]

Erythema migrans (EM)

Erythema migrans is the most frequently encountered manifestation of early Lyme disease. [14,15] Only 50 percent of patients have antibodies at the time of diagnosis. [14] Diagnosis is based on the assessment of the skin lesion and a history of a tick bite. [16] Erythema migrans is a skin lesion with central clearing that expands, reaching a diameter of at least 5 cm. [17] General symptoms of infection such as fatigue, headache, joint pain, weakness, fever, muscle pain, and regional lymphadenopathy often accompany the skin lesion. [13] Erythema migrans can be caused by all species of the *Borrelia* genospecies complex, but most commonly by *Borrelia burgdorferi* and *Borrelia afzelii*. [16] Untreated erythema migrans typically resolves on its own, but the disease then progresses from localized to disseminated form. [16,13]

Borrelial lymphocytoma

Borrelial lymphocytoma is a rare early manifestation of infection with *Borrelia* bacteria. In most cases, it is caused by infection with the *B. afzelii* genospecies. Borrelial lymphocytoma presents as a round skin lesion, typically located on the earlobes in children and on the nipple in adults. [13]

Acrodermatitis chronic atrophicans (ACA)

Acrodermatitis chronic atrophicans is a late cutaneous manifestation of untreated Lyme disease patients. It typically appears years after the onset of infection. [18] This manifestation initially presents as an inflammatory lesion, which if left untreated progresses to a chronic atrophic phase. [19] The lesions are characterized by bluish-red or red skin changes. Fibroid nodules may appear over bony prominences, and sclerodermic lesions may develop in areas of atrophic skin. The changes are most commonly located on the extremities, and less frequently on other areas of the skin. [20] In ACA, a chronic immune reaction occurs involving T lymphocytes and CD3+ and CD4+ cells. Bacteria from the *Borrelia* genospecies bind to extracellular matrix proteins, activating metalloproteases and leading to extracellular matrix degradation. Additionally, these bacteria have a high affinity for collagen fibers. Collectively, the damage to connective tissue, including collagen degradation, leads to skin atrophy. Complications of ACA may include neuropathy, bacterial superinfections. Acrodermatitis chronica atrophicans is considered a risk factor for the development of skin cancers such as squamous cell carcinoma, basal cell carcinoma, and B-cell lymphoma. [19] Despite appropriate treatment, relapses are common. [18]

Neurologic manifestations

Neuroborreliosis is a rare clinical manifestation resulting from Lyme disease. [21] It occurs in approximately 15% of untreated patients. [22] However, it is often overlooked in the diagnosis. [21] It has been conventionally believed that spirochetes reach the central nervous system hematogenously. However, new cohort studies conducted among patients with symptoms of neuroborreliosis show that the migration of *Borrelia* bacteria to the central

nervous system occurs via peripheral nerves. [23] The most common manifestation of neuroborreliosis in US is facial nerve palsy. This is an early manifestation, and as shown by studies conducted by A. Marques et al., the median interval between the first nonspecific symptoms of developing Lyme disease infection and facial nerve palsy is 19.5 days.

This manifestation of Lyme disease is closely associated with *B. burgdorferi* infection - in most patients with palsy, there are positive antibodies against this genospecies of the *Borrelia* family. In the case of facial nerve palsy, early and accurate diagnosis and initiation of appropriate treatment are important. The greatest diagnostic challenge is distinguishing the etiology resulting from infection with *Borrelia* genospecies from Bell's palsy, often associated with herpes simplex reactivation. [22] Neuroborreliosis can also present as lymphocytic inflammation of the meninges. Symptoms include headache, cranial neuropath, neck stiffness, and sensory or motor radiculoneuritis. Cases of cerebellar ataxia and encephalomyelitis have also been described. Some genospecies of Lyme disease may induce characteristic symptoms, for example, *B. garinii* can lead to Bannwarth syndrome. [13] Bannwarth syndrome is inflammation of spinal and cranial nerve roots accompanied by meningitis. This is the most common neurological manifestation of Lyme disease in adults in Europe and the second most frequent manifestation overall, following erythema migrans. Bannwarth syndrome more commonly develops in patients whose erythema migrans was localized on the head, neck, and torso. [23] It is characterized by severe pain similar to that experienced with herpes zoster, which does not respond to traditional pain management. Within a maximum of 4 weeks, Bannwarth syndrome leads to flaccid paralysis or sensory disturbances. [24] Neuroborreliosis can also manifest as cerebrovascular events and vasculitis. The most common symptom is ischemic stroke, less frequently TIA, and cerebral venous sinus thrombosis. [25] Ocular symptoms can also suggest the presence of Lyme borreliosis in a patient. In systematic review B. E. Lindström BE et al. in pay attention to ocular symptoms like visual deterioration which appear in a patient infected with *Borrelia* bacteria. [2] Also In this case report [26], bilateral optic nerve swelling without accompanying pain, associated with visual impairment, is described in case of Lyme borreliosis infection.

Lyme carditis (LC)

Lyme carditis is a rare manifestation of untreated Lyme disease. [27,23] It is estimated that the incidence in Europe ranges from 0.3 to 4%, and in the United States from 4 to 10%. Symptoms of Lyme carditis typically occur within one week to seven months after the appearance of erythema migrans or transmission of infection. In some cases, the cardiac manifestation is an isolated symptom of infection with a genospecies from the *Borrelia* family, while more commonly it is accompanied by skin, neurological, and joint involvement. Bacteria from the *Borrelia* genospecies, after colonizing muscle tissue, activate an immune response. This response is excessively amplified and, according to studies on murine models, is associated with the presence of IgM antibodies against spirochete antigens. As a result of the cross-reaction, cardiac muscle proteins are also destroyed. The symptoms of Lyme carditis are non-specific and heterogeneous. Patients with this condition may present with symptoms such as lightheadedness, dyspnea, and chest pain. [28] In the vast majority of cases—up to 90%—Lyme carditis clinically manifests as atrioventricular block

(AVB). [27,28] Characteristic features of atrioventricular block caused by the invasion of muscle tissue by bacteria from the *Borrelia* genospecies include significant variability in severity—from first to third degree block—and intermittency. [28] However, pacemakers are rarely required for patients with Lyme carditis. In most cases, they are used as temporary support during antibiotic treatment. Antibiotics are highly effective in treatment. Following the treatment algorithm, symptoms of the block resolve in the majority of patients. [27] Other rare conditions that can be caused by infection with *Borrelia* spirochetes include myocarditis, endocarditis, and pericarditis. These clinical manifestations can be asymptomatic or present only with non-specific chest pain. [28]

Lyme arthritis

Lyme arthritis is the most common late manifestation of untreated Lyme disease. [29] This stage of infection typically occurs several months to several years after being bitten by an infected tick and affects 60 percent of patients who have not received any treatment.[30] Inflammatory changes most commonly affect the knee, less frequently other joints such as the elbow, wrist, and hip. [29,31] The typical symptoms include warmth, pain, and swelling, which occur intermittently or persistently. [32] The lack of exacerbation of pain during weight bearing and passive and active joint movements in the affected joint is a distinguishing feature from bacterial inflammation. [29] In most patients, antibiotic treatment is effective and the inflammation resolves. However, in a small number of patients, despite the eradication of *Borrelia* bacteria, there is a worsening of symptoms and the development of so-called Post-infectious Lyme arthritis. In these patients, synovial hyperplasia has been observed, accompanied by an autoimmune reaction involving B and T cells. This disease entity is treated like other autoimmune forms of arthritis. [32]

Post treatment Lyme disease syndrome (PTLDS)

Post treatment Lyme disease syndrome is a syndrome that develops in patients who have undergone treatment for Lyme disease. [12] The pathophysiology of PTLDS is unknown, and the diagnosis of this disease entity is controversial in the medical community. [33] The symptoms of the syndrome develop in approximately 10% of patients and include chronic fatigue, widespread musculoskeletal pain, and cognitive difficulties. [12] Additionally, difficulties with sleep and paresthesias may occur. [33] These disturbances must persist for at least 6 months, and their onset must be within 6 months of the diagnosis of Lyme disease and the recommended treatment. [13] However, the diagnosis is often given to patients who have been exhibiting medically unexplained physical symptoms for a prolonged period without correlation with other Lyme disease symptoms. [34] The available literature indicates the risk of frequent overdiagnosis of PTLDS, which exposes patients to unnecessary treatment that may carry side effects. Additionally, overdiagnosis delays the diagnosis of high-morbidity diseases such as neurological, psychiatric, and rheumatological disorders. On the other hand, some physicians consider this medical condition controversial and as a result, patients often seek help from informal doctors who recommend uncertified tests and inappropriate therapy. In a study conducted by S. Prat et al., it was observed that antibiotic treatment for PTLDS does not provide benefits in alleviating symptoms. Additionally, due to the lack of a gold

standard in the treatment algorithm, prolonged therapy may lead to adverse events such as diarrhea, sometimes with the presence of *Clostridium difficile*, electrolyte disturbances, anaphylactic reaction, bacterial and fungal superinfections, and consequently sepsis.[12]

Treatment

The chemiotherapeutics used in the treatment of Lyme disease are antibiotics, which have been utilized for this purpose for many years. The general treatment algorithm involves the use of orally administered amoxicillin, cefuroxime, doxycycline, and intravenously administered ceftriaxone. The meta-analysis conducted by Jiaru Y. et al. indicates that effective treatments for erythema migrans include cefuroxime, azithromycin, amoxicillin, doxycycline, and oral cephalosporins. [35] Other skin manifestations like ACA can also be treated with these antibiotics. [19]. When it comes to the treatment of neuroborreliosis, antibiotics are also commonly used and they demonstrate high effectiveness. Antibiotics used in the treatment of neuroborreliosis include intravenous ceftriaxone, oral doxycycline, oral amoxicillin, penicillin, cefotaxime, and cefuroxime. [35]. An analysis conducted by Marques A. et al. shows that antibiotics have a high efficacy in treating facial nerve palsy. Out of 38 patients studied, 34 fully recovered. They also evaluated combined therapy with corticosteroids, and the results indicate that these drugs do not accelerate the healing process. [22] In the study conducted by Lindström B.E. et al. indicates that the most effective drugs in the treatment of ocular Lyme disease are also antibiotics such as oral doxycycline or intravenous penicillins and cephalosporins administered for a period of two to three weeks. [2] On the other hand, a study conducted by Y. Lu et al. shows that administering corticosteroids in bilateral optic neuritis is highly effective, however, the treatment algorithm should never omit the use of antibiotics. [26] Bannwarth syndrome should also be treated with antibiotics. A case report described by Y. E. Omotosho et al. demonstrates that early diagnosis and initiation of appropriate treatment are crucial in preventing disease progression. In the patient they described, a 21-day course of intravenous ceftriaxone was administered, resulting in complete recovery within 3 weeks. [36] Vascular episodes in the central nervous system resulting from Lyme disease infection, like other manifestations of Lyme disease, show a significant response to antibiotic treatment. The chemotherapy agents commonly used should be intravenous ceftriaxone for two to three weeks. In some cases, corticosteroids or immunosuppressive agents such as cyclophosphamide may be added to the therapy, especially when vasculitis is diagnosed in the patient. [25] During spirochetal treatment, Jarisch-Herxheimer Reaction (JHR) may develop. This inflammatory complication arises within 24 hours of the first dose of antimicrobial treatment against *Borrelia* species. Treatment of this reaction involves administering corticosteroids. [2] Treatment of Lyme carditis also relies on the use of antibiotics. However, when patient has a high-degree AV block, pacemaker implantation may be necessary—either temporary or permanent. [27] Sometimes Lyme carditis may resolve spontaneously, without any treatment. [28]. Another manifestation of Lyme disease, also treated with antibiotics, is Lyme arthritis. Studies show that doxycycline or amoxicillin administered for 30 days is effective. However, some patients may require a

longer treatment cycle to achieve satisfactory results. This is typically the case for patients who still experience minor joint swelling after the initial treatment cycle. [29] The latest manifestation of Lyme disease is Post Treatment Lyme Disease Syndrome. Its underlying mechanism is unclear, making its treatment controversial. However, antibiotics are most commonly used for its treatment.

The most frequently used antibiotics include doxycycline, ceftriaxone, cefotaxime, cefuroxime, penicillin, and dapsone. In a meta-analysis conducted by Zhang X. et al., a study was cited in which patients diagnosed with PTLDS were treated with oral doxycycline, hydroxychloroquine, and clarithromycin. The results indicated that this treatment did not have a positive effect on health-related quality of life. In contrast, another study included in the meta-analysis evaluated the efficacy of intravenous ceftriaxone and the assessment of fatigue using the FSS-11. The results indicated that this treatment was effective, and patients experienced reduced fatigue. [37] Currently, there is no evidence that bacteria from the *Borrelia* genus persist in tissues after the recommended treatment regimen for infection has been applied. [33] Additionally, overdiagnosis of PTLDS often leads to unnecessary therapy, exposing patients to side effects. An article by Prat S. et al. cites adverse effects of long-term high-dose antibiotic treatment, including electrolyte disturbances, diarrhea complicated by *Clostridium difficile* infection, bacterial and fungal infections, and sepsis. In many cases, these complications require hospitalization, significantly impacting patients' quality of life. Another drug used off-label in the treatment of PTLDS is disulfiram. This substance lacks efficacy for this condition, and its use is associated with serious side effects.[12] Therefore, additional research is needed in the areas of diagnosis and treatment of post-treatment Lyme disease syndrome. [37]

Summary

Lyme disease is the most common tick-borne illness, widely prevalent and affecting individuals across different age groups and regions. However, a common factor among these individuals is frequent exposure to open spaces from March to November, when the risk of being bitten by a tick infected with *Borrelia* bacteria is highest. Therefore, the most effective method of preventing infections is to avoid exposure by covering the body with clothing or using appropriate repellents. The infection can present with a variety of manifestations. Due to the multitude of symptoms, which can often be nonspecific, accurate diagnosis of this condition is challenging in clinical practice. The current diagnostic algorithm consists of two tests: ELISA and Western blot. The results of these tests are often difficult to interpret definitively, and therefore should be evaluated by experienced professionals. Antibiotic treatment is effective for most clinical manifestations. Additionally, corticosteroids or cyclophosphamide are often used, especially in cases of neuroborreliosis. While much is well understood about Lyme disease, further research is needed on controversial topics such as the definitive assessment of the existence of Post-Treatment Lyme Disease Syndrome (PTLDS) and the development of potential gold standards for its treatment.

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