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The impact of Lyme disease on quality of life and multiorgan function, diagnosis, late stages of the disease and PTLDS

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Abstract

Introduction and purpose of the work:

Lyme disease is the most common tick-borne disease worldwide. It is caused by bacteria of the Borrelia genus. It is transmitted by ticks of the Ixodes genus. The disease caused by this bacteria can affect many organs of the human body. Knowledge of the diagnosis, form of the disease and treatment is necessary because this disease entity can often be encountered in clinical practice. The aim of the study is to present information on available diagnostic methods and a description of the organ form of the disease, distinguishing: articular form, cardiac form and neuroborreliosis, based on a review of the current literature.

Review methods:

The review is based on 20 articles obtained from the PubMed databases, using the keywords: "lyme disease of the joints", "neuroborreliosis", "lyme disease of the heart". Published between 2000 and 2023.

Brief description of the state of knowledge:

Lyme disease most often causes symptoms in the skin, musculoskeletal system, heart muscle and nervous system. Diagnosis of the disease is based on the clinical symptoms presented by the patient. The key symptom of the disease is the presence of Erythema Migrans (EM). The articular form of Lyme disease is characterized by an ongoing inflammatory process located

within the joint. It is located within large ponds. The most common cardiac form of the disease is self-limited Lyme carditis. However, in the course of neuroborreliosis, meningitis is observed. Treatment is based on antibiotic therapy.

Conclusions:

Lyme disease is a life-threatening disease. It may cause non-specific symptoms, so it is important to diagnose it as early as possible and implement treatment to prevent progression.

Keywords: Lyme Arthritis, Neuroborreliosis, Lyme Carditis

Introduction

Lyme disease is caused by the bacteria *Borrelia burgdorferi*. It is the most common vector-borne disease in the United States and one of the most commonly diagnosed tick-borne diseases worldwide [1,2]. Lyme disease can also be caused by other species of the Borrelia genus such as *B. garinii* and *B. afzelii*. Regardless of the species, these bacteria are transmitted by ticks from the Ixodes genus [3, 4]. Lyme disease was first described in the United States and is named after the place where it was officially identified. Although it was first described in the US, the disease was already known in Europe to present with dermatological and neurological symptoms, unlike the mainly rheumatologic clinical picture described in the US [3]. It is also one of the most common diseases transmitted by arthropods in the northern hemisphere in temperate climates. Lyme disease is a multi-stage disease that can affect multiple organs in the human body

During the course of the infection, the disease can manifest symptoms in the skin, joints, heart muscle, and nervous system [5]. The most common symptoms presented by patients are erythema migrans (EM) at the site of the tick bite, headache, fever, and fatigue [4]. Erythema migrans is a common symptom in many patients, but not in all cases. It usually appears within seven to ten days after contact with the infected vector at the site of the bite. EM may be accompanied by flu-like symptoms such as fever, joint pain, muscle aches, or fatigue. Due to the fact that Lyme disease does not always present with characteristic symptoms and can mimic a viral illness, it can delay diagnosis and treatment [6]. If the symptoms are nonspecific and the disease is not quickly diagnosed and treated, it can progress, leading to neurological,

cardiac, and joint symptoms in the patient [4]. The most common symptoms associated with the development of neuroborreliosis in patients include painful meningitis (Bannwarth syndrome) and lymphocytic meningitis [5].

Diagnostics

Laboratory diagnosis of *B. burgdorferia* infection is based on the detection of specific antibodies in a two-step process. The first stage is the use of an enzyme-linked immunoassay (EIA), and then the tested sample is subjected to Western-Blot analysis. This test is not sensitive in the early stages of Lyme disease development, so a negative result does not guarantee the exclusion of *B. burgdorferia* infection [3].

Serological tests aimed at detecting antibodies against Borrelia are not reliable due to the antibiotic therapy used. For this reason, the diagnostic diagnosis should be based on the clinical symptoms presented by the patient [7]. Polymerase Chain Reaction (PCR) is used to diagnose bacterial DNA, and the material used for testing is blood, cerebrospinal fluid or synovial fluid collected from the patient. The disadvantage of this diagnostic method is the low sensitivity of the test [8].

The articular form of Lyme Arthritis (LA) can be diagnosed on the basis of antibodies against *B. burgdorferia* detected in the serum. Detection of *B. burgdorferia* DNA by PCR in synovial fluid or synovium is a critical diagnostic criterion for LA in the course of Lyme disease [7].

The diagnosis of Lyme carditis includes the diagnosis of erythema migrans with a diameter of at least 5 cm. An additional criterion in the absence of erythema is the occurrence of at least one symptom of the musculoskeletal system, e.g. joint swelling, or one symptom of the nervous system, e.g. meningitis with symptoms of peripheral nerves. Additionally, a positive laboratory test for *B. burgdorferia* infection is required [8].

The diagnosis of neuroborreliosis is based on the examination of cerebrospinal fluid. Each case of neuroborreliosis is characterized by inflammatory changes in the cerebrospinal fluid [9]. Pleocytosis is the basic diagnostic criterion of neuroborreliosis [5]. Normal cerebrospinal fluid is observed only in the very early stages of the disease. Specific IgM antibodies against Lyme disease are detected in the blood only from the third week after exposure, and IgG antibodies from the sixth week of infection [9].

Articular form of borreliosis

Out of all species of the genus Borelia. *B. burgdorferii* has the greatest potential to damage the cartilage of articular surfaces. The basic pathomechanism of LA is the perivascular accumulation of lymphocytes, macrophages and mast cells observed in the interstitium during histopathological examination in patients with severe articular Lyme disease. Th1 lymphocytes and the cytokines INF-γ and, to a lesser extent, interleukins 4, 10 and 12 play an important role in creating the inflammatory reaction in the joints. There is increasing evidence that Th17 lymphocytes also participate in the pathomechanism of LA development. Recent studies show that *B. burgdorferii* affects the expression of aggrecan, directly contributing to damage to the cartilage of articular surfaces. The ongoing damage to the cartilage of the articular surfaces during the course of the disease intensifies the active inflammatory process in the affected joint.

Pain in the joint most often appears between four days and two years after the tick bite. The average time to onset of skeletal symptoms is approximately six months in the US. In Europe, these symptoms appear slightly earlier. They develop over a period of ten days to sixteen months. LA is diagnosed practically only in patients who have not been treated for Lyme disease. Starting antibiotic therapy a few days after diagnosing the infection virtually eliminates the possibility of LA. The disease usually affects one or more large joints and is asymmetric. LA usually develops in more than five joints. Characteristic symptoms are pain and inflammation in the joint [10]. The skin is excessively warm, red and there is visible swelling in the joint. A significant number of patients also report limitations in the range of movements in the affected joints. In the course of ongoing inflammation in the joints, changes located in the synovial membrane, tendons and tendon entheses are also observed [7]. LA most often affects the shoulder, elbow, ankle and wrist joints. Some patients also report fatigue and malaise [10].

Treatment for adults with LA includes oral doxycycline, amoxicycline, or cefuroxime for 28 days. Patients with recurrent arthritis with moderate or severe symptoms can be treated with ceftriaxone administered intravenously for two to four weeks [7].

Post-infectious arthritis

Some patients who suffered from arthritis in the course of Lyme disease did not achieve a satisfactory therapeutic effect after antibiotic treatment. Instead of complete healing of the joints, patients complain of persistent inflammation of the synovium, which intensifies after the end of antibiotic therapy. In these patients, the histological picture shows massive proliferation and fibrosis of synovial fibroblasts, cellular infiltration, proliferation of blood vessels and obliterative microvascular changes. This picture resembles that of rheumatological arthritis (RA) with greater microvascular destruction. The inflammatory process may be accompanied by thickening of the tendon sheaths and calcification of the tendons. Unlike RA, post-infectious arthritis usually disappears in all patients within one to two years [11].

Lyme carditis

This disease develops in the course of Lyme disease when bacteria present in the blood of an infected person settle in the heart muscle tissue. Carditis correlates with symptoms of the skeletal or nervous system [8]. Studies show that myocarditis occurs in Europe in 0.3% to 4%, while in the United States it occurs in 4% to 10% of untreated patients with Lyme disease [12]. This percentage was higher in cases of asymptomatic carditis. Most cases of Lyme carditis occur between June and December [8]. The median diagnosis is 21 days from the onset of infection, but the average time from the onset of symptoms ranges from several days to seven months [12]. This disease is more common in men. The disease particularly affects people aged 5 to 14 and 44 to 59. Carditis is much more common in North America than in Europe. Moreover, it has not been confirmed that patients with underlying heart disease have a higher risk of cardiac complications of Lyme disease [8].

An urgent indication for performing an ECG is in patients suspected of having heart inflammation in the course of Lyme disease in order to detect or exclude atrioventricular block. The most common form of the disease is self-limited Lyme carditis with a transient disturbance in the conduction of nerve impulses stimulating the heart, inflammation of the pericardium and myocardium [13]. If the PQ interval is longer than 300 ms, patients require continuous monitoring. In 90% of cases, there are disturbances in the conduction of electrical impulses necessary for the proper functioning of the heart. Symptoms of pericarditis occur in 60% of patients [14]. Cardiac dysfunction is in most cases reversible and disappears after antibiotic therapy, and a small percentage of patients require pacemaker implantation [15].

Neuroborreliosis

The specificity of the Borrelia strain plays a key role in the development of infection of the central nervous system, to which the spirochetes enter the bloodstream or ascend through the peripheral nerves. Fourteen to eighteen days after the tick bite, spirochetes can be detected in the cerebrospinal fluid, contributing to the gradual development of neuroborreliosis [4].

About one third of patients remember being bitten by a tick. Taking a thorough history of the patient regarding EM may be crucial in determining whether the patient has had contact with a tick. About half of patients in Europe suffering from neuroborreliosis remember that they had a clinical symptom of erythema migrans. Early neuroborreliosis most often develops between two and eighteen weeks after tick infection and may be the only symptom of the disease. In Europe, the most common clinical form of neuroborreliosis is painful lymphocytic meningitis. The most common clinical manifestation of the disease is the appearance of pain. In approximately one fourth of diagnosed patients, pain is not observed as the first symptom of the disease. The pain is sharp and stabbing, which intensifies at night. Paresis of the limbs occurs in approximately two thirds of patients with meningitis. More than half of the patients also present symptoms related to the cranial nerves, most often involving the facial nerve. This is one of the most common symptoms observed in the course of acute neuroborreliosis in diagnosed patients in the USA.

Lymphocytic meningitis occurs especially in children and adolescents. Meningitis in children is particularly dangerous because it can lead to increased intracranial pressure and the appearance of pseudotumor of the brain [5].

Ocular form of Lyme disease

In the course of Lyme disease, in some cases the eyeball may be affected. Optic neuritis has been reported in both Europe and the United States. The incidence ranges from 4% to 27% among patients depending on the studies. The most common accompanying symptoms are headaches and scotoma. In addition to eye problems, there are also ailments related to the nervous system, such as paresthesia and ataxia. Additionally, joint pain, muscle pain and fatigue are also observed [16]. The medical history includes a tick bite. Fundus examination

reveals optic disc swelling associated with meningitis [17]. All patients responded well to treatment with corticosteroids in combination with antibiotics or with antibiotics alone [16].

Post-treatment Lyme disease syndrome (PTLDS)

These are symptoms occurring in patients who have undergone antibiotic therapy against Lyme disease. Cognitive dysfunctions are observed in the form of fatigue, fibromyalgia-like pain, and even depression, which leads to a deterioration of the quality of life in properly managed patients, lasting for more than 6 months and may accompany the patient for the next years of his life [18]. The number of patients affected by this syndrome is approximately 10% of Lyme disease patients. The incidence of cases has increased significantly over the last few years. Risk factors include female sex, a long period preceding treatment, and high mononuclear cell infiltration in the cerebrospinal fluid before the end of antibiotic therapy [3]. Currently, no effective method of causal treatment of this syndrome has been discovered. Therapy is based on the use of antidepressants, painkillers and psychotherapy [19]. To prevent exacerbations of neurocognitive symptoms, it is recommended to discontinue medications that may cause them. Drugs that worsen cognitive dysfunction include opioids, benzodiazepines, anticholinergics, antihistamines and proton pump inhibitors [20]. Moreover, it has not been proven that PTLDS is associated with chronic *B. burgdorferia* infection. Studies in this direction were conducted in which one group of patients received ceftriaxone intravenously for thirty days and then oral doxycycline for sixty days. The second group of patients received a placebo infusion for thirty days and then an oral placebo also for sixty days. The study results showed no differences in laboratory test results between the groups. However, improvement in mood and somatic complaints was noted in both groups without significant differences between the research groups [19].

Disclosure:

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