

Editorial
Od RedakcjiINFECTIONS CAUSED BY *BORRELIA BURGENDORFERI SENSU LATO*ZAKAŻENIA WYWOŁYWANE PRZEZ *BORRELIA BURGENDORFERI SENSU LATO*

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Introduction

Lyme disease is a multisystem illness caused by an infection with the spirochete *Borrelia burgdorferi sensu lato*. The illness is identified in many countries in the Northern Hemisphere [1], but the risk of infection is determined by geographical location and the frequency of occurrence of spirochetes in animal reservoirs and vectors. Among European countries, Lyme disease occurs most frequently in Germany, Austria, Slovenia, Sweden and Poland [2]. In Western Europe, a great variability in the frequency of occurrence is observed. Lyme disease has been most frequently diagnosed in Sweden with 464 cases per 100,000 inhabitants and least frequently in Italy with 0.001 per 100,000 inhabitants [3]. According to the data of Polish National Institute of Public Health - National Institute of Hygiene, the incidence of Lyme disease is systematically increasing. In 2013 12,754 of cases of Lyme disease were registered (incidence rate 33.1 per 100,000 inhabitants) [4] and in 2014 this number increased to 13,870 (incidence rate 36.0 per 100 00 inhabitants) [5]. The highest incidence rates in 2013 and 2014 were observed in the Podlasie region, 100.2 per 100,000 inhabitants and 106.8 per 100,000 respectively [4,5]. The preliminary epidemiologic data show that in the period from January to December 2015 13,624 cases of Lyme disease were diagnosed in Poland (incidence rate 35.4 per 100 000 inhabitants) [6].

Genospecies of the complex *Borrelia burgdorferi sensu lato*

The family of *Spirochaetaceae* encompasses the following species: *Borrelia*, *Spirochaeta*, *Cristispira*, *Treponema* and *Leptospira*. *Borrelia* is a genus of bacteria which includes spirochetes causing relapsing fever (*Borrelia recurrentis*) and spirochetes *Borrelia burgdorferi* causing Lyme disease. The complex of closely related species of *Borrelia* genus transmitted by ticks and connected with Lyme disease are referred to as *Borrelia burgdorferi sensu lato* (*B. burgdorferi* s.l.) [7]. This complex includes 18 genospecies of which *B. burgdorferi sensu stricto* (*B. burgdorferi* s.s.), *B. garinii*, *B. afzelii* and *B. bavariensis* have been considered human pathogens. Spirochetes *Borrelia spielmanii* has been considered potentially pathogenic for humans [2]. In the Netherlands, Germany, Hungary and Slovenia they were isolated from *Erythema migrans* (EM) skin lesions [8]. *Borrelia bissettii* was isolated from patients with Lyme disease, DNA *B. valaisiana* was identified in cerebrospinal fluid of patients with neuroborreliosis and EM. *Borrelia lusitaniae* was isolated from patients with suspected Lyme disease, however there have been some suggestions that clinical symptoms in those infections are not the same as in the case of Lyme disease [2,9].

So far in the USA only one genospecies- *B. burgdorferi sensu stricto* has been identified as responsible for causing Lyme disease. However, research conducted by Pritt et al. [1] in the years from 2003 to 2014 led to the discovery of a new genospecies which was included into the complex *Borrelia burgdorferi sensu lato*. Infection with a new bacteria, for which a name *Borrelia mayonii* was proposed, has been identified so far in six patients with Lyme disease symptoms (five blood samples, one synovial fluid sample). In total, 100,545 diagnostic samples from patients from Minnesota, Wisconsin, and North Dakota were examined. The tests indicated that *Borrelia mayonii* is genetically different from bacteria *Borrelia burgdorferi sensu stricto*. *Borrelia mayonii* was detected in *Ixodes scapularis* ticks which were collected in the area where the examined patients lived and where they were exposed to the contact with ticks [1,10].

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Vectors of *Borrelia burgdorferi* sensu lato

Ticks of *Ixodes* genus have a key role in transmitting spirochetes *Borrelia burgdorferi* sensu lato from animal reservoirs to human body [2]. Vectors transmitting spirochetes are various *Ixodes* genera depending on continental location. In Asia *B. burgdorferi* s.s., *B. garinii*, *B. afzelii* and *B. valaisiana* are transmitted by *I. persulcatus* or *I. hexagonus*, however in North America *B. burgdorferi* s.s is transmitted mainly by *I. scouparis* but also by *I. pacificus* and *I. affinis* [11,12,13]. In Europe, the vector of spirochetes *B. burgdorferi* s.l. is a tick *Ixodes ricinus* which apart from Europe can be found in Asia Minor and north-western part of Africa where it is the vector of the only one species- *B. lusitaniae* detected there. In the area around the Arctic Circle, *B. garinii* is transmitted among animal reservoirs, mainly birds, by *I. uriae* [11,12,13,14].

Diagnostics and clinical manifestations of Lyme disease

The diagnostics of Lyme disease is based on three criteria- the history of tick bites, patients' clinical symptoms and the results of serological tests (Elisa, Western blot) indicating the presence of specific antibodies IgM/IgG anti-*B. burgdorferi* [15]. Clinical symptoms of Lyme disease can be divided into two categories- early stage symptoms and late stage symptoms. In 80 per cent of those infected there is a skin lesion- Erythema chronicum migrans (*Erythema migrans*, EM) in the place of tick bite, multiple Erythema migrans is very rarely observed. Erythema may appear in the period from three to thirty days after an infectious tick bite and subsides in a few days or up to four weeks without the need to treat it with antibiotics but it is not synonymous with the eradication of the infection. Erythema migrans has a diagnostic value and doing serological test for Lyme disease is not recommended at that time [2,16,17]. Early neuroborreliosis manifests itself within a few weeks after the moment of infection and gives the following symptoms- meningitis, inflammation of facial nerve or other cranial nerves and nerve roots inflammation. These symptoms may be accompanied by a headache, fatigue, hyperesthesia or neck stiffness which are not diagnostic criteria when they occur separately [2,17]. Early stage joint symptoms in Lyme disease (*Lyme arthritis*) include swelling, limited joint mobility- most frequently the knee joint and less frequently the hip joint, the shoulder girdle, the elbow joint and the carpus. Early stage symptoms of Lyme disease also affect the heart muscle (*Lyme carditis*) and those symptoms may manifest themselves within the period of one week up to seven months after the moment of infection. Clinical symptoms may take the form of an atrioventricular block, cardiac arrhythmia, myocarditis or acute pericarditis. Those symptoms may develop in the early stage of infection when EM is still visible or after its resolution. *Borrelial lymphoma* is a very rare skin manifestation of an infection with *B. burgdorferi*. This livid lesion is located on an ear lobe, a nipple or scrotum. However, it occurs in only two per cent of the patients approximately after two months and it more frequently affects children than adults [2,15,18].

Clinical manifestations of early stage Lyme disease are accompanied by the presence of the anti-*B. burgdorferi* antibodies in blood serum (IgM and/or increasing titer IgG). In the case of neuroborreliosis, the presence of specific antibodies or DNA of bacteria can also be found in cerebrospinal fluid. In the case of *Lyme arthritis*, the presence of *B. burgdorferi* DNA can be found in synovial fluid.

Encephalomyelitis, meningitis and peripheral polyneuropathies are the clinical symptoms of late stage neuroborreliosis. The above-mentioned symptoms must be differentiated from those in multiple sclerosis. Multiple sclerosis can be excluded through testing cerebrospinal fluid and blood serum for the presence of IgM i IgG anti- *B. burgdorferi* antibodies. In the late stage of the illness, the symptoms of *Lyme arthritis* are also intensifying [2]. If untreated, late joint symptoms of Lyme disease lead to cartilage and bone erosion and synovial hypertrophy. Many years after the infection with *B. burgdorferi*, acrodermatitis chronica atrophicans (ACA) may occur which manifests itself with red skin lesions located on distal parts of limbs and on face and trunk, ulceration may also occur [2,15,17]. Late clinical symptoms of Lyme disease may be accompanied with the presence of IgG anti-*B. burgdorferi* in serum in high titers and in the case of neuroborreliosis also in cerebrospinal fluid [2].

Genospecies of *B. burgdorferi* s.l. versus symptoms of Lyme disease

According to Hubal et al., clinical differentiation of the course of Lyme disease is not only caused by the effectiveness of immunological system of the patient but also the characteristics of genospecies of the complex *B. burgdorferi* s.l. [19]. This assumption seems to be proven by the specificity of infections caused by the newfound spirochetes *Borrelia mayonii* which is responsible for spreading Lyme disease in the United States. The infection with *Borrelia mayonii* is commonly associated with high spirochetemia which is uncharacteristic of infections with other genospecies of the complex *B. burgdorferi* s.l. Fast-moving spirochetes were observed in the blood

samples from one patient however, bacterial cultures were grown from the blood samples of two patients [1,10]. The data basing on the analysis of the test results of first six patients prove that the symptoms of infection with *B. mayonii* are to some extent similar to those caused by *B. burgdorferi*. Similarly to *B. burgdorferi*, *B. mayonii* in the early stage of the infection (a few days after the exposure) causes pyrexia and headache, erythema occurs in the later stage (a few weeks after the exposure), joint pains. Unlike *B. burgdorferi*, the infection with *B. mayonii* seems to be connected with other symptoms such as nausea, vomiting and dispersed rash. It is suggested that the immunological response in the infections with *B. mayonii* is similar to the infections with *B. burgdorferi*, therefore two-stage diagnostics characteristic of Lyme disease can be employed in identification of the infections, in some justified cases PCR tests for *B. mayonii* can be done. PCR tests proved the utility of gene *oppA1* in diagnosing those infections [1,10]. Patients infected with *B. mayonii* were treated with Doxycycline, Amoxicillin, Ceftriaxone i Cefuroxime achieving good therapeutic effects [10].

It is believed that *B. garinii* is most often responsible for generating neurological symptoms of Lyme disease and *B. afzelii* is more often responsible for skin symptoms such as acrodermatitis chronica atropicans and borrelial lymphoma. The infection with *B. burgdorferi* s.s. is connected with greater possibility of occurring joint symptoms [9,20,21,22]. Genospecies *B. burgdorferi* s.s., *B. afzelii*, *B. garinii*, *B. spielmannii* and *B. valaisiana* may cause erythema chronicum migrans [8,9].

The effectiveness of eradicating *B. burgdorferi* infection

Elimination of Lyme disease symptoms as a result of antibiotic therapy may prove their effectiveness, however specific anti-*B. burgdorferi* antibodies can still be present in the serum [21]. The presence of antibodies, without clinical symptoms, cannot be considered as indication for treatment, therefore serological tests which determine the level of IgM/IgG anti-*B. burgdorferi* antibodies should not be used for the evaluation of treatment effectiveness [17].

Peptide C6 of the VlsE lipoprotein *B. burgdorferi* was treated as a factor in the evaluation of effectiveness of antibiotic therapy and eradication of infection [23]. However, views on this issues are not explicit. Fleming et al. found that patients with post-treatment Lyme disease syndrome (PTLDS) had low titers of anti-C6 antibodies whereas patients with the symptoms of Lyme disease have high titer levels [24]. Embers et al. examined rhesus macaques infected with *B. burgdorferi* which after the period of four to six months were treated with antibiotics. Xenodiagnostic methods, cultures, molecular methods and the evaluation of the level of Peptide C6 *B. burgdorferi* were among the methods employed in the tests. A considerable decrease of antibody titer level for C6 was observed in all animals treated with antibiotics. Moreover, the results prove the fact that spirochetes may survive in the tissues of some infected animals. The authors suggest that the lack of correlation between the response for C6 and the presence of spirochetes may have various causes. Another explanation is that spirochetes stay in the body and anti-C6 antibodies titer does not indicate their presence perhaps because of the fact that bacteria lost lp28-1 plasmid [25]. The questions of potential survival of *B. burgdorferi* in human body after antibiotic therapy, reinfection and persistent infections are still being discussed. Owing to the molecular methods, it was proved that the recurrence of EM may be connected with a new infection as a result of tick bite and it is not necessarily connected with the persistence of infection. It is recognized that the DNA fragments of *B. burgdorferi* may remain for a very long period after an effective antibiotic therapy and eradication of live spirochetes. However, it has not been clarified yet whether the permanence of antigens of eradicated bacteria may lead to the long-term stimulation of human immunological system and finally to non-specific symptoms. It is thought that PTLDS concerns patients with persistent and non-specific symptoms such as joint pains, fatigue, an impairment of cognitive functions for more than six months after the end of treatment for Lyme disease [26]. Moreover, attempts have been made to introduce xenodiagnosis as a method of detecting *B. burgdorferi* in humans. Patients with various symptoms of infection with *B. burgdorferi* (treated for Lyme disease, PTLDS and those with finished or ongoing treatment for Erythema migrans) participated in the tests for which pathogen-free tick larvae *I. scapularis* were used. Those tests revealed the presence of *B. burgdorferi* DNA in one of the patients treated with antibiotics for EM and in one patient with PTLDS [27]. Moreover, in order to analyze *B. burgdorferi* infection, animal models are used. It is assumed that they may be the basis for concluding that spirochetes remain present in the tissues despite antibacterial treatment [25]. However, while interpreting them, several factors need to be taken into account- route of infection, *B. burgdorferi* infectious dose for humans, differences in pharmacokinetic and pharmacodynamic parameters for animal and human antibiotic therapy and the differences in immunological response of various animal species taking into account the fact that many animals are natural reservoirs of *B. burgdorferi* [26].

Animal infections with *Borrelia burgdorferi*

Many wild animals are natural reservoirs of the complex *Borrelia burgdorferi* sensu lato thus they do not have any detectable symptoms. However, some domestic animals like dogs may display similar symptoms connected with *Borrelia burgdorferi* infection to those that humans have. It was observed that dogs may have difficulties in moving, pyrexia, swollen lymph glands, joint inflammation and neuroborreliosis at the late stage of the disease [28].

European Union Concerted Action on Lyme Borreliosis (EUCALB) informs that *B. burgdorferi* infections may be common in a few domestic animals species but for the time being there are no proofs for the occurrence in any of the species except for the dogs. Most *B. burgdorferi* infections in horses are asymptomatic, however seroprevalence in this species is 50 per cent in certain areas. Clinical cases are rare and laminitis, joint swelling and uveitis are among the observed symptoms. It is possible that the number of infection cases is underrated for non-specific character of symptoms. In Switzerland, one case of *B. burgdorferi* s.s. and *B. afzelii* infection was proved in cattle owing to real-time PCR method. The infection was accompanied with the following symptoms-erythema located on the udder, weight loss, legs swelling, joints swelling, stiffness of gait, acute laminitis and multiple joints inflammation. For the time being, there are no sufficient data to assess the risk of developing *B. burgdorferi* infection symptoms in cats [16].

Summary

It is justified to systematically monitor the number of those infected with Lyme disease in European countries and conduct the research on spreading of genospecies *B. burgdorferi* s.l. in animal reservoirs and vectors. Moreover, it is essential to take action for increasing the society's awareness of tick-borne diseases prophylaxis. It is very important due to the observed increase in the number and activeness of ticks which leads to the increased risk of infection with spirochetes *Borrelia burgdorferi* sensu lato and other pathogens transmitted by these vectors.

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