

## Lyme disease: etiology, pathogenesis, clinical courses, diagnostics and treatment

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### ABSTRACT

Lyme disease (LD) is caused by *Borrelia burgdorferi*, transferred by infected ticks *Ixodes ricinus*. LD occurs endemically in Europe, America and Northern regions of Asia. In Poland, LD is the most frequent tick borne disease, which causes serious epidemiological problems. The main health hazard of LD occurs on the forested areas of Podlasie, Maritime province, the West Poland lake district, and Carpathians. The highest incidence 114.0 per 100 000 was registered in Podlaskie province. The infectious cycle of *Borrelia burgdorferi* includes: nymph moults to adult, eggs laid by female, eggs hatch to larva, larva feeds on first host, fully fed larva drops to ground, larva moults to nymph, nymph attaches to and feeds on the second host. LD is a chronic disease attacking many organs, including the skin, heart, brain and joints. LD is divided into three stages based on clinical symptoms: I - limited infection (Erythema

migrans and *Borrelia lymphoma*), II - disseminated infection (numerous erythema migrans, early neuroborreliosis, joint inflammation, Lyme carditis), III - late borreliosis (chronic atrophic limbs inflammation, late neuroborreliosis, chronic joint inflammation). At present, the best diagnostic method for LD is a labor- and time consuming two-stage serological method. First-line antibiotics in the treatment of Lyme disease are doxycycline, amoxicillin, cefuroxime axetil, ceftriaxone, cefotaxime, and penicillin G. The best method of avoiding *Borrelia burgdorferi* infection is to avoid biting from ticks carrying spirochetes. Early removal of ticks, protects against spirochaetal infection.

**Key words:** Lyme disease, etiology, pathogenesis, clinical courses, diagnostics, treatment.

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## Etiology of the Lyme disease

LD is a bacterial disease caused by spirochete *Borrelia burgdorferi*, which is transferred by infected ticks *Ixodes ricinus* (the common tick) [1-3]. Spirochetes penetrate the human skin in 48 hours after the bite from infected ticks, and after 72 hours, there are 100% risk of spirochete infection [4].

The spirochete *Borrelia burgdorferi* belongs to Spirochetaceae family [3]. *Borrelia burgdorferi* is Gram-negative micro aerobic, slowly growing spiral-shape bacteria. *Borrelia burgdorferi* cells divide every 12-24 hours [5-7]. Complex *Borrelia burgdorferi sensu lato* consists of 12 genospecies [3]. Between 11 genospecies of the *Borrelia burgdorferi sensu lato* complex, appearing in wild animals and transferred by ticks, three are certainly pathogenic for humans: *B. burgdorferi sensu stricto*, *B. garinii* i *B. afzelii* – all appear in Europe. In North America *B. burgdorferi sensu stricto* is present exclusively, and in Asia appear *B. garinii* i *B. afzelii*. *B. bissettii*, *B. valaisiana* and *B. lusitaniae* are potentially pathogenic for humans. The presence of the different spirochete genospecies in Europe and USA is considered to be a reason for different clinical manifestations of LD [8,9].

It was reported that particular genospecies demonstrate specific organ predispositions. *Borrelia burgdorferi s. stricto* predispose to Lyme arthritis. *Borrelia garinii* – most frequently causes neuroborreliosis, and *Borrelia afzelii* causes chronic limb dermatitis [10].

## Epidemiology of the Lyme disease

Lyme disease is an endemic, prevalent tick borne disease in Europe, Northern regions of Asia and North America [11]. In Europe, LD is prevalent in forested areas of Scandinavia, Central Europe, particularly in Germany, Austria and Slovenia [12,13]. Australia, Africa, South America and southern states of USA are considered free from LD [11]. In Poland, LD is the most common tick borne disease which creates serious epidemiological problems [13,14] (Figure 1). The main health hazard of LD occurs on the forested areas of Podlasie, Maritime province, the West Poland lake district and Carpathians [12].

LD is characterized by broad spectrum of multiorgan clinical symptoms [3]. Visitors to endemic territories: woodland workers, that collecting wild fruit or mushrooms, are predominantly those exposed on LD [11,15]. LD may develop at any age, with the same frequency in women and men [11]. Between forestry workers in Poland from the Lublin macro region, antibodies against *Borrelia burgdorferi* in blood serum were detected in 27.7% of the group, from Białowieża 43.4%, from Karkonosze 67% [16]. In the Podlasie

region, greater relapse of LD was registered than in the rest of Poland: in 2000 years, it was 6.72 times higher, and in 2002, it was 5.59 times higher, than the national average. In the Podlasie region during the period 1996-2002 morbidity on LD amounted to 15.05-16.66% of Poland's morbidity. In Poland, the highest morbidity for LD (19.95%) was noted for the eastern and central regions of Podlasie, and the lowest in the west region of Podlasie (6.7%) [17]. Specific antibodies against *Borrelia burgdorferi* appear in 11-13% of healthy persons in Poland, which indicates the contact of these persons with spirochetes and asymptomatic course of LD [18]. In Poland (according to National Institute of Public Health, State Institute of Hygiene) LD morbidity is systematically growing. Paradowska-Stankiewicz and Chrześcińska [19] published data that in 2009, 10 329 cases of Lyme borreliosis were reported in Poland, more about 20% than in the last year and more about 25% higher incidence-27.1 per 100 000, and above two times more than the median incidence in 2003-2007. The highest incidence 114.0 per 100 000 was registered in Podlaskie province. Of total Lyme borreliosis cases 2 504 were hospitalized.

The highest activity of ticks *Ixodes ricinus* (common tick, European forest tick) is noted in May-June and September-October. Increase in LD morbidity from July to October is related to the greatest activity of ticks [16]. In the saliva of *Ixodes ricinus* substances acting as anticoagulants (e.g., eicosanoids), analgesics, factor restraining macrophages migration, anti-inflammatory substances (e.g. PGE<sub>2</sub>) are present. *Ixodes ricinus* saliva may contain neurotoxins and pathogenic microorganisms. Pathogenic microorganisms may take shelter in the salivary gland of ticks (e.g. viruses) or in the intestine of *Ixodes ricinus* (e.g. *Borrelia burgdorferi*) [18].

The highest risk of spirochete *Borrelia burgdorferi* infection is connected with the nymph stage of spirochetes. Adult spirochetes are large, more visible and easier to remove than nymphs. Infection of humans takes effect by rubbing tick vomits or saliva, during the tick's feeding process [20].

Fortunately, for humans not every *Ixodes ricinus* is infected with *Borrelia burgdorferi* [12]. In Poland, the percentage of infected ticks amounted from 4% to 58.3% [21] and not every contact of human with an infected tick brings LD. Only 1-3% of persons bitten by infected ticks develop LD [12].

## Pathogenesis of *Borrelia burgdorferi* infection

Spirochete *Borrelia burgdorferi* is highly invasive. The pathogenicity of *Borrelia burgdorferi* depends on the spirochete's mobility, cytotoxicity, antigenic variability, lymphocyte stimulation and

the resistance of spirochetes to complement activation in the absence of specific antibodies [22].

*Borrelia burgdorferi* are transferred from the place of infection to different tissues of the host with blood, lymph, per continuum as a result of plasminogen activation, and by peripheral nerves. Inflammatory symptoms are visible more frequently at the site of the tick-bite, which indicates that dissemination is more effective in tissue than blood [22-24]. *Borrelia burgdorferi* spirochetes undergo adhesion to endothelial cells as well as to components of the extracellular matrix, and migrate through an endothelial layers to the extracellular matrix. Localization of *Borrelia burgdorferi* in the extracellular matrix and utilization of fibrocytes and lymphocytes B, hide *Borrelia burgdorferi* from the host defense system and antibiotics. Spirochetes *Borrelia burgdorferi* display tropism to heart connective tissue, synovial membrane, vascular endothelium as well as to ligaments and tendon attachments. In infected tissue's *Borrelia burgdorferi* form characteristic agglomeration centers [22,25].

A change in the surface antigens enables *Borrelia burgdorferi* to escape from elimination at the initial period of infection. In *Borrelia burgdorferi* survival, superficial Osp proteins play an important role, which protect membranous proteins against antibody action [24].

*Borrelia burgdorferi* spirochetes are able to modify immunological response (both cellular and humoral) as well as to decrease phagocytosis of the infected organism [22,23,25]. *Borrelia burgdorferi* disturbs the secretion of cytokines and antibodies, by aggregation with fibroblasts and tissue proteins. *Borrelia burgdorferi* may directly attack and destroy T and B lymphocytes [23].

*Borrelia burgdorferi* may activate chemotactic elements by induction of interleukins (IL): IL – 1, IL – 6, IL – 8, IL – 10, mediators of inflammation, immunological complexes, and activate the complement system [26]. In the case of LD infection complement is activated through both the classical and alternative routes, however, antibacterial action is only activated in the presence of specific anti-*Borrelia* antibodies. Complement may nodulate some species of *Borrelia burgdorferi*. A phenomenon called „microbiological adherence” may happen independently of the presence of antibodies [26]. In the pathogenesis of LD fusion of the spirochetes with glycosaminoglycans: heparin, heparan sulfate (enables fusion of spirochetes with endothelium), and dermatan sulfate (enables fusion of spirochetes with glial cells) play an important role. Furthermore, decorin (skin proteoglycan) is recognized by bacterial lipoproteins [24]. *Borrelia burgdorferi* decreases phagocytosis by disturbance of the phagocyte cell membranes and leakage of cytotoxic substances from the cytoplasm of phagocytic cells into patient

blood [23]. Phagocytosed spirochetes are removed from the host by oxygen dependent and independent processes [24]. In oxygen, dependent processes reactive oxygen and nitrogen species: hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), singlet oxygen, etc., as well as halogenate derivatives are involved. In oxygen independent phagocytic process's hydrolases (e.g., proteases and glycosidases) located in lysosomes of phagocytes [23,24] are involved.

### LD infection course and major clinical manifestation

Lyme disease is a multi-organ and multi-systemic chronic disease with a diverse clinical pictures [23, 27]. Asbrink i Hovmark [14] divided LD into three stages [20,26,28] based on the clinical picture [2]:

- Early borreliosis
- Limited infection (stage I):
- Erythema migrans,
- Borrelia lymphoma
- Disseminated infection (stage II):
- Numerous erythema migrans,
- Early neuroborreliosis,
- Joint inflammation,
- Lyme carditis
- Another (retinitis, chorioiditis),
- Late borreliosis
- Chronic atrophic limbs skin inflammation,
- Late neuroborreliosis,
- Chronic joint inflammation.

### Erythema migrans

Erythema migrans occurs in about 60% of infected persons, independently of age and sex. Erythema migrans looks like an oval, red or blue, painless stain occurring at the site of the tick bite. Erythema with a diameter larger than 5 cm has diagnostic value. Several weeks after the tick bite, erythema migrans gradually enlarges in size. In the middle of the red oval a bright spot (picture similar to a target appears). Erythema migrans may reach a diameter up to 70 cm. Erythema migrans usually lasts several weeks and then disappears. However disappearance of erythma does not mean eradication of LD [27,29]. The serological diagnosis of erythema migrans is not essential in the typical course of erythema migrans, as for diagnosis the presence of characteristic skin stain in connection with tick bite in anamnesis is sufficient [8,30,31,32]. Numerous erythema migrans only appear rarely, and indicate dissemination of infection. Numerous erythema migrans are smaller than the original erythemas and are uniformly stained [33]. Skin changes of the Erythema migrans may be accompanied by systemic symptoms as: fever, pain of muscles and joints,

headache, sometimes meningeal signs and enlargement of the lymph nodes, which may be treated as certificate of spirochetemia [8,9,20, 31,32].

### **Borrelia lymphoma**

Borrelia lymphoma (previously named Lymphocytic skin lymphoma) occurs very rarely (in about 5% of patients) [25]. Borrelia lymphoma forms painless red or blue-red nodes [29] 1 – 5 cm diameter in skin or subcutaneous tissue, composed mainly of lymphocytes B [20]. In the majority of cases Borrelia lymphoma occurs up to 10 months after the tick bite [29]. Borrelia lymphoma appears most frequently on the ear concha, nose, mamilla, aureola of the mamma, and scrotum [3]. In differential diagnosis one should take into account skin lymphoma, foreign body, sarcoidosis, neoplastic metastases, periostitis, and contact dermatitis [27].

### **Neuroborreliosis**

Neuroborreliosis is the most frequent form of disseminated infection of *Borrelia burgdorferi* in Europe, but is less often found in the USA. Neuroborreliosis involves both the central and peripheral nervous system. All three species of *Borrelia burgdorferi* may cause neuroborreliosis. In Europe *Borrelia garinii* (72%), are isolated more frequently from cerebrospinal fluid than *Borrelia afzelii* (28%), and *Borrelia burgdorferi sensu stricto* [8,9, 31,32]. In the early disseminated stage, neuroborreliosis may proceed with paralysis of cranial nerves, most frequently as facial nerve paralysis. Paralysis may be accompanied by inflammatory changes in cerebro-spinal fluid. The early stage of neuroborreliosis may be manifested by paralysis of nerve roots or single peripheral nerves, meningitis, encephalitis or encephalomyelitis. But the late stage LD may appear as: slow course *encephalomyelitis* with involvement of the white matter. Neuroborreliosis may proceed as peripheral neuropathy with dysphasia, parestheses, radiculalgias, and sometimes with pareses or as chronic encephalopathy with dominating impairment in memory and concentration, irritation, sleepiness and changes in personality [8,9,30-32].

### **Lyme arthritis (LA)**

Lyme arthritis is a frequent manifestation of *Borrelia burgdorferi* infection. LA appears both in the early disseminated stage of LD and the late stage of infection. In the USA about 60% of non-treated patients with infection caused by *Borrelia burgdorferi sensu stricto*, present transient symptoms of arthritis affecting one or more joints. In Europe where *Borrelia garinii* and *Borrelia afzelii* are infectious factors, arthritis is observed in only 3% to 15% of patients. About 10% of LA patients present persistent arthritis which is resistant

to antibiotics, with persistent symptoms of LA, despite administration standard antibiotic treatment. Even frequently repeated antibiotic treatment may be ineffective, which is caused by the persistence of spirochetes in joints or the persistence of arthritis despite elimination of pathogens. Differentiation between persistence of spirochetes to antibiotics and arthritis without spirochetes is possible by detection of the *Borrelia burgdorferi* DNA in synovial fluid or synovium [8,9,31,32]. LA may present with different clinical forms: **1.** as migrating osteoalgia, arthralgia, myalgia, tenalgia in a period of several weeks from infection, **2.** as recurrent osteoalgia, arthralgia, or peri-arthritis manifested for months or years with long periods of idiopathic remissions. **3.** as recurrent or chronic, usually asymmetrical arthritis with pain, swelling and enhanced warming of joints manifested usually after two years after infection. Most frequently LA attacks the knee joint, less often the humero-shoulder joint, elbow, wrist joint, hip, ankle joint, rarely the temporo-mandibular joint, and small joints of hands and legs. LA may proceed with multiple aggravation episodes, interrupted by periods of remission. LA may display a tendency to idiopathic remission. In rare cases LA causes irreversible permanent damage to attacked joint and permanent joint immobilization [8,9,30-32].

### **Lyme carditis**

Lyme carditis is observed in 4% to 10% of patients from North America and in 0.5% to 4% patients from Europe. Males suffer more frequently than females from Lyme carditis. Lyme carditis appears at the early disseminated stage of LD, on average about 21 days from the start of infection, however this period may last from one week to 7 month. Heart troubles in *Borrelia burgdorferi* infection may be single or appear in connection with another forms of the LD as erythema migrans or symptoms from motor and nervous systems.

A characteristic feature of heart involvement in the course of *Borrelia burgdorferi* infection is the acute onset and atrio-ventricular dissociation as I or II degree atrio-ventricular block, or total atrio-ventricular block as well as block of the division of bundle branch or block propagation of impulses of atrio-ventricular system. Less often Lyme carditis may lead to myocarditis, pericarditis, benign cardiac insufficiency, chronic hemostatic cardiomyopathy. Myocarditis may be caused by the presence of *Borrelia burgdorferi* in cardiac muscle during spirochetemia which appears comparatively early. Less often Lyme carditis may proceed in the form of myocarditis or pericarditis [8,9,30-32].

### **Chronic atrophic dermatitis**

Chronic atrophic dermatitis presents as red or blue-red stain occurring on the skin of the distal parts of limbs, after several or a dozen or so

years after infection (average after 10 years). It is a chronic, long standing, usually progressive form of LD described more frequently in Europe than in the USA, affecting older patients, more frequently in men than women. Most frequently chronic atrophic dermatitis is caused by infection of *Borrelia afzelii*, less frequently by *Borrelia burgdorferi sensu stricto*, and *Borrelia garinii* [8,9,30-32].

### Diagnosics of Lyme disease

Diagnosis of LD is based on a history of tick bites and clinical symptoms. Laboratory diagnostic of LD is based on a „two-stage diagnostic protocol” consisting of ELISA and Western-blot determination the specific anti-*Borrelia* antibodies. In the modern serological tests (so-called third generation tests) recombinant antigens are used, particularly protein p83/100 (indicator of the late stage of LD), p41int (the internal part of the flagellin molecule, which has a relatively minor role because of cross-reactions with flagellin of other bacterial species), proteins of the external leaflet of the cell membrane OspA, OspC, p39 and proteins p17, p58, p14, p30 and p43. Applied tests should contain the VlsE antigen (common to different species of spirochetes or contain antigens of the all three pathogenic genospecies *Borrelia burgdorferi s. lato*. In the first month of LD infection determination of the IgM response gives highest sensitivity. In the later stage of diagnosis should be confirmed by detection of specific IgG. Two to four weeks after infection, immunoglobulins of the IgM class are found, reaching a peak at six weeks, and their titer drops over 4-6 months. Whereas IgG antibodies occur at 6 to eight weeks after infection, and remain many years after infection, displaying a slow decay in titer, as determined by ELISA or Western-blot. Serological methods enable univocal discrimination of active *Borrelia* infection from status after disease. False-positive results are found mainly with IgM antibodies, which appear in persons suffering from other bacterial diseases (e.g. bacterial infections, infectious mononucleosis, cytomegaly) and non infectious diseases (e.g. auto infectious diseases). Tests which detect antibodies reacting with *Borrelia burgdorferi* confirm the presence of LD, but alone are not enough to diagnose LD [8,31,32,34].

Diagnosis of neuroborreliosis must be confirmed by the presence of pleocytosis in cerebrospinal fluid and intrameningeal production of antibodies against *Borrelia burgdorferi* both in IgM and IgG class. However, no antibodies may be detected in the early stage of LD and criterion better diagnosis of neuroborreliosis is the presence of pleocytosis in cerebrospinal fluid [8,30-32,34,35].

Diagnosis of *Borrelia burgdorferi* infection by detection of *Borrelia burgdorferi* DNA by the PCR method, looks very promising. The most important limitation of the PCR method concerning diagnosis of borreliosis is the lack of standardization. However, for diagnostics of borreliosis qualitative PCR examination is sufficient. In practice, for PCR examination material derived from slice of skin taken from erythema migrans of limb, synovial fluid, or cerebro-spinal fluid is recommended. PCR examination of blood, is not recommended because of its low sensitivity.

**False-positive results** in serological diagnostics of LD are found with 5-8% of the healthy population [35]. False-positive results [36] are connected with: **1.** screening without confirming tests **2.** Cross reactions with *Treponema pallidum*, Ehrlichia, Herpes virus's antigens. Cross reactions refer mainly IgM antibodies caused by some borrelia antigens, which occur numerously on other microorganisms. Cross reactions may be verified in Western-blot tests, **3.** Hypergammaglobulinemia.

**False negative results** in serological diagnostics of LD may be caused by: **1.** Serological investigation performed too early [37]. It should be mentioned that to obtain a reliable result from serological investigation, blood should be collected after two months after exposition to *Borrelia burgdorferi* [3]. In the case of a negative result in the early stage of *Borrelia burgdorferi* infection testing with a fresh sample after four weeks from the manifestation the first symptom of LD is recommended [29], **2.** Immunodeficiency in the patient **3.** Presence of immunological complexes. In the case of massive *Borrelia burgdorferi* infection, bacterial antigens may bind circulating antibodies, and such complexes are not detected by serological methods, **4.** Local production of antibodies. Antibodies may be produced exclusively in cerebrospinal fluid or synovial fluid. Such localization of antibody production may prevent their detection and determination in blood serum. **5.** Influence of antibiotic therapy at beginning of the LD, **6.** Intracellular residence of the *Borrelia burgdorferi* [36].

### Treatment and prophylactics of the Lyme disease

In Poland, standard methods recommended by Polish Society of Epidemiology and Infectious Diseases for LD treatment are used [38]. During selection of the appropriate treatment duration and stage of LD infection should be considered [29]. Antibiotic therapy of the LD lasts a minimum 21 days [35].

First-line antibiotics in the treatment of Lyme disease are doxycycline, amoxicillin, cefuroxime axetil, ceftriaxone, cefotaxime, and penicillin G. In the case of contraindications or intolerance to the use of doxycycline or amoxicillin, may be used azithromycin or clarithromycin. LA should not be treated with: first-generation cephalosporins, fluoroquinolones, karbanemens, vancomycin, metronidazole, tinidazole, trimethoprim-sulfa-methoxazole, benzathine penicillin, fluconazole. Furthermore, is not recommended: combination therapy with antibiotics, the pulse administration of antibiotics and many months lasting treatment with antibiotics [36,39].

The best method of avoiding *Borrelia burgdorferi* infection is to avoid biting from ticks carrying spirochetes [26]. Early removal of ticks, protects against spirochaetal infection [10,25]. For removing tick's use of special plastic pincers, which are available at pet shops is recommended.

During tick removal one should manipulate with care, neither press nor grease. Careless removal of ticks may cause regurgitation of the tick gut content, which increase the probability spirochete transmission to humans. Ticks should be removed with one movement, and the bite immediately thoroughly disinfected [2]. After removing the tick, the injured person should be thoroughly observed up to 30 days, looking for symptoms of LD. If a rash or another symptom of LD appears on the victim's skin, the person should be inspected by a physician [26].

Active prophylactics of LD (e.g. vaccination) is not available in practice [33]. In the USA, an anti-*Borrelia burgdorferi* vaccine was developed and registered based on protein A of the external envelope of spirochete (Osp A), but in 2002 this vaccine was removed from the market [28].

## CONCLUSION

In conclusion, it should be stated that LD, the most widespread tick transferred disease in Europe, still creates many diagnostic and therapeutic problems. The best prophylactic method for avoiding LD is repelling ticks and/or immediate and careful removal with immediate disinfection of the bite area. To date, antibiotic therapy reduces most of the clinical symptoms, protects against complications as well as the chronic course of infection, and inhibits dissemination of the spirochetes. Complicated cases of LD require a more comprehensive diagnostic approach using new methods such as the determination of exoglycosidases in serum, synovial and/or cerebrospinal fluids.

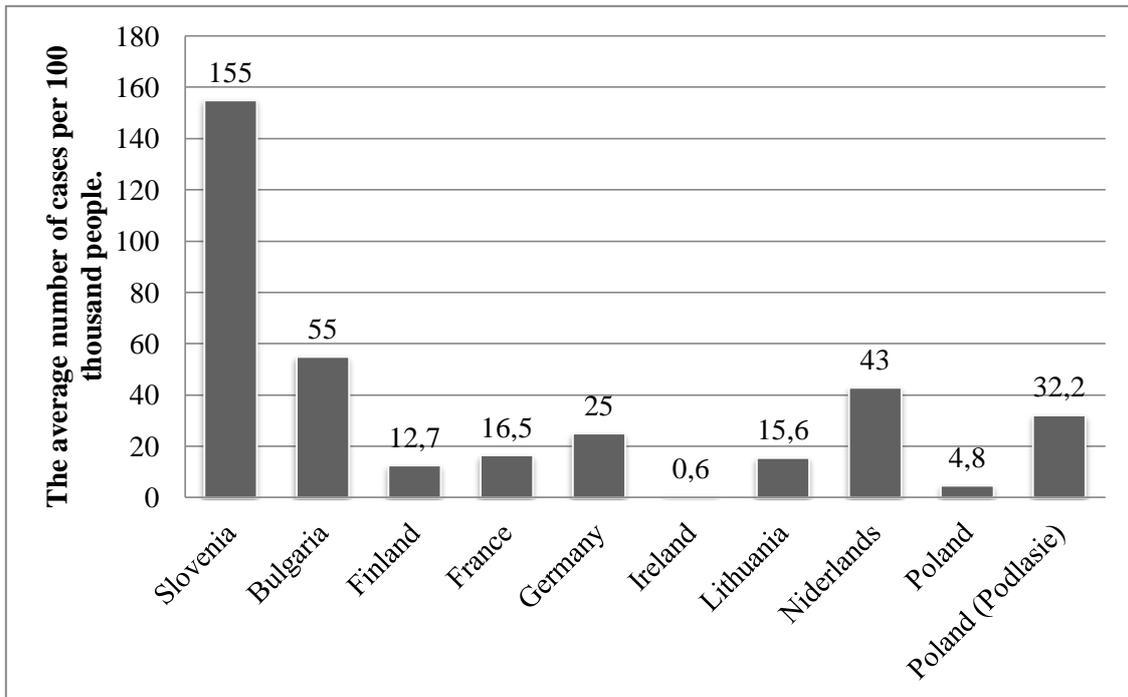
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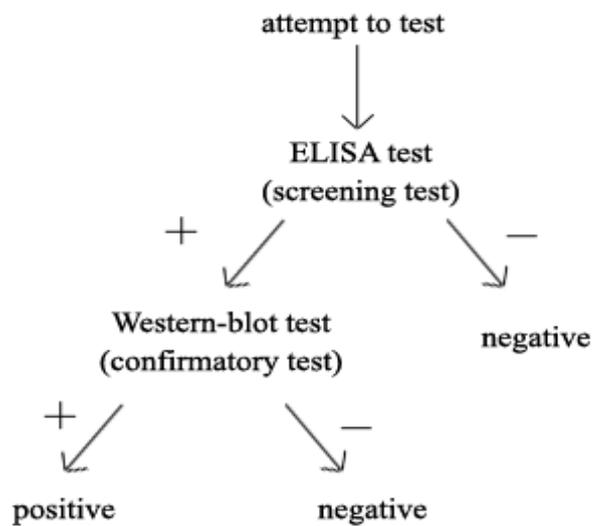
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**Figure1.** Annual incidence of Lyme disease in selected European countries [13].



**Figure 2.** Serological diagnostics of Lyme disease [38].