UKRAINIAN JOURNAL OF VETERINARY SCIENCES

2022. Volume 13, No. 1. P. 61-70

Received: 25.10.2021 Revised: 16.01.2022 Accepted: 23.02.2022

UDC: 616-022.7:579.834.114
DOI: 10.31548/ujvs.13(1).2022.61-70

The History of the Discovery and Research of Lyme Borreliosis in Animals and Humans

Nataliia Soroka*, Oksana Kravchuk, Olena Zhurenko

National University of Life and Environmental Sciences of Ukraine
03041, 15 Heroiv Oborony Str., Kyiv, Ukraine

Abstract. The relevance of this study is conditioned upon the substantial importance of the history of the discovery and research of Lyme borreliosis for medical science and veterinary medicine, since new theories, experiments, conclusions are built on the research of scientists who have proved the existence of this disease in animals and humans, and positive practices are accumulated regarding methods and schemes of treatment and prevention. The purpose of this study was to analyse the literature primary sources covering the history of the discovery, the results of the study of Lyme borreliosis disease to understand the features of its course and search for effective diagnostic and treatment methods. The chronology of the main results confirming the existence of Lyme borreliosis caused by Ixodidae ticks is summarised. Scientific sources covering the history of the discovery and research of Lyme borreliosis were analysed to understand the features of its course and search for effective methods of laboratory diagnostics and treatment. The main projects of the European Union programme aimed at financing research and innovative development "Horizon 2020" were determined. It was found that the projects in the field of Lyme borreliosis research also relate to certain topics, namely the creation of tests for the detection of Lyme disease, the study of the vectors of the causative agents of this disease, the development of an appropriate vaccine, and the assessment of the risks of consequences for human and animal health. It was concluded that the main areas of research are as follows: persistence of diseases and their causative agents transmitted by Ixodidae ticks; natural control of Ixodidae ticks; detection of pathogens in Ixodidae ticks; level of infection of vertebrates; habitats and natural foci of vectors and their hosts; testing and medical trials; effect of magnetic field on Borrelia; genome mapping of Borrelia species, visualisation of the human brain for disease research; research by polymerase chain reaction; endocrine studies; immune complexes, diagnosis of neuropsychiatric complications in children and adults. The practical value of this study lies in the awareness of modern scientists about the chronology of the study of Lyme borreliosis, the main ways of distribution and methods of its diagnosis in animals and humans, determining the prospects for further research according to the topical issues covered in this paper, which are solved within the framework of international projects

Keywords: Ixodidae ticks, Borrelia, spirochaetes, Ixodidae tick bites

Suggested Citation:
Soroka, N., Kravchuk, O., & Zhurenko, O. (2022). The history of the discovery and research of Lyme borreliosis in animals and humans. *Ukrainian Journal of Veterinary Sciences*, 13(1), 61-70.

**Corresponding author*

Introduction

Lyme borreliosis is a transmissible, naturally occurring disease that is transmitted by Ixodidae ticks and caused by borrelia (spirochetes). Most often, *Borrelia burgdorferi* is detected, which is transmitted between Ixodidae ticks and their hosts – animals and humans [1]. According to A. Afzelius (1910) [2], A.C. Steere (1977) [3], W. Burgdorfer (1984) [4], N.M. Magpies, V.V. Nedosekov et al. (2020) [5], this disease is described by a variety of clinical symptoms, as well as a tendency to a chronic and latent course in both humans and animals. The natural reservoir of Borrelia (spirochetes) is most often mouse-like rodents, birds, and deer, less so – cattle, dogs, and other animal species [2; 3; 4]. However, the disease had a long history of its discovery, justification, and proof of existence [5].

This paper is devoted to a retrospective of the development and analysis of studies of Lyme borreliosis in animals and humans. The study highlighted the key issues that were investigated by scientists during studies of various diseases in mammals, which gave them the opportunity to draw conclusions about the existence of Lyme borreliosis disease and ways of infection with the pathogen. The analysis of various scientific sources covering the history of the discovery and the results of the study of Lyme borreliosis disease provided an opportunity for scientists to identify the features of the course of this disease and search for effective diagnostic methods and treatment methods.

The historical aspect of the study of Lyme borreliosis was investigated by Ukrainian scientists: V.Yu. Klius (2018) during the study of clinical and instrumental features of chronic forms of Lyme disease with a predominant lesion of the nervous system and improvement of their treatment tactics in humans [6]; I.I. Ben (2019) [7] during working on the definition of clinical and epidemiological characteristics of human granulocytic anaplasmosis and creating an algorithm for diagnosing this disease; V.A. Levytska et al. (2021) in her research on the animal body protection system on transmissible diseases [1]; foreign scientists: M.P. Littman et al. (2018), provided recommendations for the diagnosis, treatment, and prevention of Lyme borreliosis in dogs and cats [8], A.G. Barbour and R.S. Gupta (2021) investigated spirochaetes of the Borrelia genus, especially their morphology, biology, as well as vector and pathogenicity for vertebrates to identify phylogenetic data confirming their conservation by reptiles, monotremes, and birds [9]. Researchers J.R. Bobe et al. also analysed Lyme disease prevention and control methods and considered other issues in this area that have not yet been studied (2021) [10]. X. Zhuang, X. Yang and others (2018) investigated one of the determinants of *Borrelia burgdorferi* virulence, designated in the study as Lmp1 and is a surface, conserved and potential multi-domain protein that takes part in various functions during the invasiveness (infectivity) of Borrelia (spirochaetes) [11; 12].

The purpose of this study was to analyse the literature sources that cover the history of the discovery of Lyme borreliosis, methods for diagnosing this disease and the search for effective treatment.

The objectives of this study were to analyse the state of the issue, its research in scientific publications; to summarise Ukrainian and foreign practices in the historical aspect of the occurrence of Lyme borreliosis, to describe the chronology of research in this area and introduced methods for detecting pathogenic pathogens in Ixodidae ticks.

Results and Discussion

Retrospective analysis of Lyme borreliosis studies

The history of the discovery of Lyme borreliosis begins in 1909, when the Swedish botanist Adam Afzelius described a case of chronic migratory erythema in a person, which occurred at the site of a tick biteRetrospective analysis of Lyme borreliosis studies

The history of the discovery of Lyme borreliosis begins in 1909, when the Swedish botanist Adam Afzelius described a case of chronic migratory erythema in a person, which occurred at the site of a tick bite [5; 9]. A few years later, the Austrian dermatologist B. Lipschutz [9] described similar clinical manifestations in another patient that lasted 7 months and proposed to call them "chronic migratory erythema" (erythema chroniicum migrans, ECM) due to the long-term course.

In further studies, scientists described headaches and neurological disorders, cases of chronic lymphocytic meningitis [13; 14] in humans that occurred after attacks of Ixodidae ticks. Thus, in 1922, two French neurologists, Ch. Garin and B.A. Paralysis [13] from Lyon provided the first description of neurological complications in humans after an attack of Ixodidae ticks and skin lesions. They reported a 58-year-old man who developed reddened, painful, and swollen skin lesions accompanied by inguinal lymphadenopathy a few weeks after being attacked by Ixodidae ticks. This was followed by bilateral gluteal pain, intercostal pain, and finally painful unilateral right shoulder plexopathy with deltoid amyotrophy. The serological test for syphilis (Wasserman test) was weakly positive. The researchers ruled out syphilis as the cause of the clinical manifestations and provided a medical history as an example of "paralysie par les tiques" (tick paralysis), or disorders that can be caused by a tick-borne virus, but the cause was attributed to ticks of the Dermacentor genus, while the patient was found to have *Ixodes hexagonus* [5].

In 1930, S. Hellerstrom [14] recognised a causal relationship between attacks and bites of Ixodidae ticks described by dermatoses and neurological manifestations [15]. In 1941-1944 A. Bannwarth [12] in Germany reported 14 patients who suffered from severe body, leg, and arm pain after being attacked by Ixodidae ticks, facial paralysis, and lymphocytic meningitis. However, the researcher at that time did not establish a link between a previous Ixodidae tick bite, migrating erythema, and neurological disorders, and instead preferred allergies and rheumatism.

The cause of migrating erythema remained unclear and unfounded. At the same time, S. Hellerstrom [14] and W. Burgdorfer et al. [16] testified to the role of spirochetes in the development of erythema migrans, which at that time was investigated by C. Lenhoff [17], a member of the Dermatology Clinic at the Karolinska Institute. He claimed to have developed a staining technique based on the interaction of mercuric chloride with spirochaetes, which enabled him to identify "spirochaete elements" in many human skin lesions of unknown aetiology, including psoriasis, chickenpox, lymphadenosis (benigna cutis), and "erythema-migrant" among other diseases. It turned

out that his staining method is suitable for demonstrating spirochaetes in culture but is not suitable for identifying them in smears or in areas of tissue damage with migrating erythema.

In 1943, B. Bäfverstedt [18] reported on benign lymphadenosis in humans, which developed as a result of an attack of Ixodidae ticks. According to D. Lipsker and B. Jaulhac (2009) [19], Ch. Brunnemann (2010) [20] at that time, researchers observed skin lesions, namely swelling and red spots. At the same time, S. Hellerstrom (1951) [21], E. Binder et al. [22], H. Götz [23], reported that the bite of *I. ricinus* causes oedema and erythema in humans. However, the true aetiology remained unclear until arthritis and erythema were discovered and investigated by scientists in the northeastern United States [24].

More than six decades after the first report by A. Afzelius, in the 1970s [2], W.E. Mast, W.M. Burrows (1976) investigated an unusual epidemic of oligoarticular rheumatoid arthritis in children, adolescents, and adults in Lyme, Connecticut (USA) [25]. At the same time, professor of rheumatology at Harvard University in Lyme, Connecticut (USA) A.C. Steere [3], studying 39 children and 20 adults, found an extraordinary incidence of juvenile idiopathic arthritis, which occurred after an attack of Ixodidae ticks and was often combined with migratory ring-shaped erythema.

Thus, in the 1970s, the number of cases of spotted fever has increased in people who visited or lived in Rocky Mountain Cities [4] (in the southern and north-eastern United States; in Long Island and other coastal areas of New England, and the Massachusetts offshore islands). This disease was called Rocky Mountain spotted fever, (RMSF). RMSF cases were documented by microbiologists W. Burgdorfer and A. Barbaur(1975, 1979, 1982, 1983, 1984) [4; 26].

In 1979, L. Reik et al. [27] identified neurological manifestations among a group of sick people affected by Ixodidae tick attacks. At the same time, neurological and cardiac disorders were added to the already known manifestations on the skin and affected joints, and, in general, a person developed a complex systemic disease [8; 28].

It is also worth paying attention to the research and development of the "Western blot" diagnostic technique, aimed at determining IgM and IgG to specific Borrelia antigens, which was carried out in the 1970s [5].

Most researchers attest that the Western blot evolved from Southern blotting developed by Edwin Southern at the University of Edinburgh in 1975 [5], then Northern blotting [29] developed by George Stark's group at Stanford in 1977 [30]. The results of these studies contributed to further improvement of methods for detecting proteins using antibodies, which improved the quality of diagnosis of Lyme borreliosis in both humans and animals [31].

Following the observations made in Old Lyme [32], a correlation was noted between skin rashes in sick people who suffered from Ixodidae tick attacks and arthritis. For epidemiological reasons, further studies have shown that erythema migrans and arthritis are tick-borne diseases and are associated with a carrier *Ixodes scapularis* [32].

Isolation of spirochetes from the intestines of *I. scapularis* ticks by W. Burgdorfer et al. [16] for the first time testified to the presence of an aetiological factor causing this disease, since these pathogenic microorganisms demonstrated a reaction with immune sera from sick people (USA) who suffered tick attacks and Lyme disease [28; 33].

Thus, the causative agent and carrier of Lyme disease were identified simultaneously. Just a few months later, similar spirochaetes were also isolated in Europe from *I. ricinus*, which is closely related to *I. scapularis* [8]. Extra studies conducted in the same and subsequent years confirmed Burgdorfer's conclusions [3; 9; 34]. In 1984, spirochaetes were named after their discoverer as *Borrelia burgdorferi* [35]. Furthermore, the disease was named after the discovery site as "Lyme borreliosis".

The existence of Lyme borreliosis caused by Ixodidae ticks is evidenced by historical data summarised in Table 1.

Table 1. Chronology of the main results confirming the existence of Lyme borreliosis caused by Ixodidae ticks

Year scientific research	Scientist, country	Results of studies confirming Lyme borreliosis
1910	Arvid Azfelius, Sweden [2]	Erythema migrans in humans are described
1913	Lipschütz, Austria [34]	The term "chronic migratory erythema" (erythema chroniicum migrans, ECM) is proposed
1922	Garin and Bujadoux, France [13]	Meningopolyneuritis in a person after an attack of Ixodidae ticks and its probable connection with erythema migrans are described
1930	Hellerström, Sweden [21]	Meningitis is described and a cause-and-effect relationship between Ixodidae tick attacks and neurological manifestations and characteristic dermatoses in humans is established
1943	Bo Bäfverstedt, Sweden [18]	Lymphadenosis (benigna cutis) is described
1944	Bannwarth, Germany [12]	Further descriptions of meningopolineuritis caused by Ixodidae tick attacks
1948	Carl Lennhoff, Germany [17]	Spirochaetes are reported in human tissue samples from biopsies (however, these were artefacts)

Table 1, Continued

1949	Hellerström, Sweden [21]	A suggestion appeared that spirochaetes may be the cause of human disease
1949	Thyresson, Sweden [37]	Successful treatment of sick people with penicillin for chronic acrodermatitis
1951	Hellerström, Sweden [21]	Successful treatment of people after attacks of Ixodidae ticks
1954	Gotz, Germany [23]	It was established that Ixodidae ticks are the carrier of chronic human acrodermatitis (Acrodermatitis chronica atrophicans)
1955	Binder et al., Germany [16]	A link was found between arthritis in humans and attacks of Ixodidae ticks
1974	K. Weber, Germany [36]	Successful treatment of people with ECM with antibiotics
1975-1979	E.M. Southern (1975) [37]; J.C. Alwine, D.J. Kemp, G.R. Stark (1977) [38]	The "Western blot" diagnostic method was developed
1983	W. Burgdorfer, USA [26]	Spirochetes were first isolated from the intestines of ticks *I. scapularis*, which confirms the aetiological factor that causes Lyme borreliosis
1985	V. Preac-Mursic [32]	Damage to the central nervous system in humans after an attack of Ixodidae ticks was described
1984-1985	F.W. Hyde, R.C. Johnson [33]	Cultivation of *B. burgdor*feri in skin samples and in fluids was developed

According to the literature, occurrence of Lyme borreliosis is geographically associated with mountainous and wet areas in Sweden, Germany, and the United States [39-41]. At the same time, these studies are becoming global in the 21st century due to environmental changes, the development of microbiology, epizootology, modern technologies, and the latest methods for diagnosing transmissible infections and infestations [5; 42].

In 1991, the Lyme Disease Association was established in the United States, [40] and in 2000 it became an official national organisation. Its mission was to promote awareness and control of the spread of Lyme disease and other tick-borne diseases; to identify and investigate complications using modern diagnostic methods; to raise and allocate funds for research and other issues related to Lyme and tuberculosis; to provide monetary support to seriously ill people with transmissible diseases and conduct educational activities. The Association's website [40] covers the following issues:

– conducting scientific conferences (archives, videos, data on requirements for scientific research, conditions of participation, etc.);

– regarding Lyme and other transmissible diseases (diagnosis, statistics, etc.);

– maps of registered transmissible diseases and their spread in the United States and other countries (https://lymediseaseassociation.org/LDA_Apps/content/Maps/index.html);

– reports on cases of Lyme borreliosis in humans;

– description of grants and requirements for scientific research submitted for grants;

– extra information for sick people (advanced methods of treatment of patients with Lyme borreliosis, methods of diagnosis, testing, characteristic and uncharacteristic clinical manifestations of the disease, treatment regimens, complications, genomics, vector transmission, certain aspects of pathogenesis, resistance of pathogens to medications, prevention measures, financing, long-term course of the disease and its impact on the general condition of the patient, care centres, etc.);

– on preventive measures for Lyme borreliosis in pets (problems that pet owners face when detecting the disease; measures and means of prevention; a list of acaricidal drugs to prevent attacks of Ixodidae ticks; diagnostic methods and approaches in the treatment of animals with transmissible diseases, etc.).

Lyme Disease Association Inc. Columbia University and the Vagelos College of Physicians and surgeons have been jointly hosting the Annual Scientific Conference "Lyme and other tick-borne diseases: research for treatment" since 2000 [41]. Each conference presents reports from more than a dozen national and international scientists and physicians who speak on a wide variety of topics, including epidemiology, information on pathogens that cause tick-borne diseases, diagnostic methods, treatments, cognitive difficulties, vaccines, veterinary problems, the spread of Ixodidae ticks, and genome mapping.

Notably, the Association awarded 122 grants for research on Lyme disease and diseases transmitted by Ixodidae ticks. In the United States, and in partnership with a branch, the Association established the world's first Centre for the study of the chronic course of Lyme disease, which was opened at Columbia University in 2007. The centre brings together researchers from various fields of medicine and veterinary medicine from all over the United States [42].

Since 1999, the Association has sponsored 20 scientific and medical conferences and 18 conferences held jointly with the Columbia University College of Physicians and Surgeons. It also funds cutting-edge research projects with more than 36 different researchers and institutions across the country, including Columbia University College of Physicians and Surgeons, Medical School of New Jersey, Fox Chase Cancer Centre, UC Davis, University of Pennsylvania, Bringham & Women's Hospital, New York College of Medicine, Rockefeller University, Tulane Regional Primate Center, University of North Florida, NIH/NASA and UDSA, etc. [42].

The results of the Association's research projects are published in 56 peer-reviewed scientific journals, such as the American Medical Association (JAMA), The Proceedings of the National Academy of Science, The Psychiatric Clinics of North America, Infection; Psychiatric Clinic of North America; Neurology, JSTBD, Clinical Microbiology, International Neuropsychological Society and Infection and Immunology; New, Infectious Diseases (CDC); Bacteriology, Entomology; Neuropsychiatry and Clinical Neurosciences; International Journal; Neuropsychological Society; Infection and immunity; Gene, Genetics and PLOS 1 [42].

According to the results of the project of the "LymeAid 4 Kids" Association, the data were used to apply for an NIH grant in the amount of 4.7 million US dollars. Considerable genome mapping, initially funded by the Association, has shown that different Borrelia species can exchange genetic material with each other, which is beneficial for their survival and probably interferes with the ability of an infected human or animal body to fight pathogens [43; 44].

Current state of diagnosis, prevention, and treatment of Lyme borreliosis in humans and animals

From 2012 to 2021, many projects related to research in the field of Lyme borreliosis are being implemented under the program of the European Union aimed at financing research and innovative development "Horizon 2020" [45]. 68 results were found for the keywords "Lyme borreliosis" on the EU website "Horizon2020" [45].

The analysed projects allowed identifying the main topics of research on this disease, the which relevance is timeless.

Thus, in projects that have won the competition in the EU Horizon 2020 programme, scientists pay attention to [45]:

– creating tests to detect Lyme disease, for example:

"DualDur: A Disruptive Diagnostic Technology that Enables for the First Time an Early and Accurate Diagnosis of the tick-borne Lyme Disease", 2018-2021, 2024, Hungary [46];

"Development of a prophylactic vaccine and diagnostic markers to prevent and diagnose Lyme borreliosis specific to Europe and North America", 2004-2007, Austria [47];

"A novel immunity-based test for early diagnosis of Lyme disease", 2016-2020, Netherlands, Germany, Austria [48];

"Highly sensitive and specific low-cost lab-on-a-chip system for Lyme disease diagnosis", 2010-2013, Spain, Germany, Portugal, Italy, Finland, Belgium [49];

"Demonstration Activities for the clinical validation of the prototype HILYSENS Lab-on-a-Chip", 2014-2016, Portugal, Spain, Germany, Italy, Sweden [50];

– research of Lyme borreliosis carriers, for example:

"Exploring the salivary transcriptome of Ixodes ricinus, the Lyme disease vector in Europe, and the potential role of its cystatins in pathogen transmission", 2010-2014, Czech Republic [50];

"Co-evolution and implementations of vector adaptation: a case study on seabird ticks and Borrelia", 2008-2010, France [51];

"Effects of co-infections on the emergence of an avian disease Mycoplasma gallisepticum", 2018-2022, Belgium [52];

"Phylogeny of borrelia genus", 1996-1999, France, Spain [53];

"Co-evolution and implementations of vector adaptation: a case study on seabird ticks and Borrelia", 2008-2010, France [54];

– development of a vaccine against Lyme borreliosis, for example:

"Development of a prophylactic vaccine and diagnostic markers to prevent and diagnose Lyme borreliosis specific to Europe and North America", 2004-2007, Austria, Czech Republic, Germany, Sweden [55];

"Functional genomics study of lysyl-trna synthesis as a target for the diagnosis and treatment of microbial infections and mitochondrial myopathies", 2000-2003, France, Ireland, Germany [56];

"Anti-tick Vaccines to Prevent Tick-borne Diseases in Europe", 2013-2018, Netherlands, Slovakia, Czech Republic, Spain, Germany [57];

– assessment of the risks of Lyme borreliosis consequences in relation to human and animal health for example:

"Lyme borreliosis in north Africa: risk assessment and implementations for tick management and for control of the human disease", 2000-2004, France, Argentina, Tunisia, Morocco, Portugal, Belgium, Switzerland [58];

"Complexity and predictability of epidemics: towards a computational infrastructure for epidemic forecasts", 2008-2013, Italy [59].

Notably, all projects that take place under the EU programme Horizon2020 have substantial results and are published in journals indexed by international databases such as Scopus and Web of Science. For instance, according to the project "A novel immunity-based test for early diagnosis of Lyme disease" [60], the following articles were published in 2020: "Allergenomics of the tick *Ixodes ricinus* reveals important α-Gal–carrying IgE-binding proteins in red meat allergy" [61].

Within the framework of the new research and prospects for studying Lyme disease, scientists propose to continue investigating the system of antigenic variations encoded in the vls system, which allows tracking genetic changes in *B. Burgdorferi* using the next-generation DNA sequencing method developed by Pacific Biosciences [62]. As evidenced by C. Winslow, J. Coburn, the mechanisms of this segmental system of gene conversion and the system of antigenic variations that enable *B. burgdorferi* to maintain invasions (infections) deserve additional study. Scientists also consider it important to identify and investigate more genes necessary for invasiveness (infectivity) and virulence of *B. burgdorferi*, which will expand the understanding of pathogen biology and contribute to the improvement of the proposed tests and vaccines [63].

Within the framework of the new EU programme Horizon Europe [64], conducted since 2021, research on Lyme borreliosis continues.

Under such conditions, researchers pay special attention to the study of the causative agent *Borrelia burgdorferi*. Thus, for example, researchers T. Casselli, A. Divan, E.E. Vomhof-DeKrey, H.L. Pecoraro, C.A. Brissette [65] conducted experiments on the infection of white mice with Lyme disease pathogens and *Borrelia burgdorferi*. A murine model of Lyme disease demonstrates that *Borrelia burgdorferi* colonizes the dura mater and induces inflammation in the central nervous system The researchers concluded that the results of such studies provide insight into the potential mechanisms of pathologies of the central nervous system (CNS) in humans and animals associated with Lyme disease, and also describe a model system that will allow future research to assess bacterial and host and environmental factors that may contribute to the severity of CNS damage by the *B. burgdorferi* pathogen [65].

Lyme borreliosis research in Ukraine

In Ukraine, the first cases of the disease in humans have been known since 1994. However, official registration of the disease began in 2000 [66]. The Order of the Ministry of Healthcare of Ukraine [66] states that 562 cases of this disease were detected in 2000-2004. According to the "List of enzootic territories of Ukraine with tularaemia, leptospirosis, other particularly dangerous infections and their prevention measures for 1999-2003" [66], among all regions of Ukraine, only in the territory of Kirovohrad and Luhansk regions, no cases of the disease were registered.

In 1995-2004, the Danylo Halytskyi Scientific Research Institute of Epidemiology and Hygiene of Lviv National Medical University [7] at the request of medical and preventive institutions conducted laboratory examinations of 1,907 sick people from 20 regions of Ukraine. At the same time, 1108 (58.1%) seropositive individuals were identified, of which the diagnosis was confirmed in 412 (37.2%) cases. It is important to note that the role of pathogens in the infectious pathology of the population was confirmed in the studies; various clinical manifestations of the disease (Afcelius erythema, ring-shaped erythema mite, acrodermatitis, chronic atrophic acrodermatitis, skin lymphadenosis, serous meningitis, radiculoneuritis, Bannwart's lymphocytic meningoradiculoneuritis (Bannwart's syndrome), chronic arthritis, etc.).

It is also important to pay attention to pharmaceutical research for the treatment of Lyme borreliosis in humans and animals. Initially, researchers and veterinary doctors chose specific therapeutic paints that proved effective for some protozoal diseases in animals caused by arthropods and Ixodidae ticks [1]. Thus, among the pharmaceutical products used in the world veterinary practices for the treatment of animals with piroplasmidosis, drugs with an active basis have received the widest recognition – Ionic associate of 4,4-(diazoamino)-dibenzimidine with N-acetyl glycinate (diminazene aceturate) [1; 67; 68]. This active substance is active against protozoan pathogens from the genera *Babezia, Trypanosoma* and *Thelleria*, and has an antibacterial and fungistatic effect. In pharmaceuticals and preparations, this active substance is combined with an antipyretic and an analgesic – phenazone (azidine, azidine-vet, batrizan, berenil, bbveriben, diamidine, neosidine, pyrosan, trypanol, etc.). In the 1970s, the above-mentioned manufacturers in their guidelines recommended using this drug in the form of injections only for productive animals (large and small cattle) in a 7% aqueous solution at the rate of 3.5 mg of diminazene per 1 kg of body weight, and for horses – 5 mg/kg. For these species of animals, it was recommended to re-introduce the drug solution after a day in the same dose [8]. Over time, Ukrainian scientists and practitioners began to introduce azidine to sick dogs in the form of a 7% solution at the rate of 3.5 mg/kg [61]. In Ukraine, the production of a drug called azidine-vet based on diminazene was first started at Brovapharma LLC in 2000 [61]. However, it was already clear at that time that not all animals could easily tolerate the above suggested doses of the drug. The animals also did not always recover. They frequently had complications from both the disease and these drugs. Therefore, veterinary doctors conducted more studies in practice and determined the effectiveness of new drugs for Lyme borreliosis.

K. Stiasny et al. conducted an experiment, which allowed determining that the most successful is the treatment of animals and humans within 24-48 h after the diagnosis of the disease [69]. They also noted that treating animals and humans with arthritis without intensive and prolonged administration of antibiotics does not contribute to recovery and restoration of limb function.

For Lyme borreliosis, according to V.F. Galat [70], the most effective are antibiotics of the tetracycline series – tetracycline, doxycycline hydrochloride, oxytetracycline hydrochloride, etc. However, other groups of antibiotics are also used, namely penicillin – benzylpenicillin sodium salt, Bicillin-1, 3, 5; ampicillin, ampiox, etc.; groups of cephalosporins – claforan, cefuroxime, cefazolin, etc. [70].

For erythema migrans, azithromycin (sumamed) is prescribed – 1 g on the first day, and then 500 mg for 4 days (children – 10 mg/kg). If a person was not treated at an early stage, then drugs are used depending on the lesions [71]:

– neuroborreliosis – ceftriaxone (or cefotaxime), 2 g intravenously for 2 weeks (sometimes up to 1 month);

– arthritis and cardioborreliosis – doxycycline 100 mg 2 times a day for 2 weeks (sometimes up to 1 month);

– chronic atrophic acrodermatitis – ceftriaxone, 2 g for 3 weeks (from 14 to 30 days) or doxycycline, amoxicillin, etc.

Currently, according to N.M. Soroka and V.V. Nedosekov [5], a vaccine has been developed for humans and animals (artificially synthesised surface protein OspA), which is considered an effective means of preventing Lyme borreliosis.

Conclusions

An analysis of historical data on the discovery and research of Lyme borreliosis allowed describing the chronology of the main results supporting the existence of Lyme borreliosis caused by Ixodidae ticks, which included the following events: the recording and description of erythema migrans in humans; definition of the term "chronic migratory erythema"; description of meningopolyneuritis in a person after an attack of Ixodidae ticks and putting forward a version regarding its connection with erythema migrans; establishment of a cause-and-effect relationship between attacks of Ixodidae ticks and neurological manifestations

and characteristic dermatoses in humans and further research of this problem; detection of Borrelia (spirochaetes) in biomaterials of people with migratory erythema and without erythema, but with nervous disorders; successful treatment of sick people with penicillin for chronic acrodermatitis and after attacks of Ixodidae ticks; establishing that the carrier of human chronic acrodermatitis is Ixodidae ticks; successful treatment of people with chronic erythema migrans with antibiotics; development of the "Western blot" diagnostic method; isolation of spirochaetes from the intestines of *I. scapularis* ticks, which confirms the aetiological factor that causes Lyme borreliosis; development of methods of cultivation of *B. burgdorferi* in skin samples and in fluids. According to these discoveries, research projects are being continued in the world practice in such areas as identifying the characteristics of the kinetics of *B. burgdorferi* colonisation and related immune reactions in the central nervous system of animals during the early and subacute stages of invasion; development and testing of immune-based tests for early diagnosis of Lyme disease; study of the influence of ecology on the genome of *B. burgdorferi*, etc.

References

[1] Levytska, V.A. (2021). *Zonal aspects of ixodid ticks Dermacentor reticulatus and Ixodes ricinus and improvement of the system of protection of animals from tick-borne diseases*. (Doctoral thesis, Lviv National University of Veterinary Medicine and Biotechnologies named after S.Z. Gzhytskyi, Lviv, Ukraine).

[2] Afzelius, A. (1910). Negotiations of the dermatological society in Stockholm, 28 Oct 1909. *Archives of Dermatological Research*, 101, 404.

[3] Steere, A.C., Malawista, S.E., Snydman, D.R., Shope, R.E., Andiman, W.A., Ross, M.R., & Steele, F.M. (1977). Lyme arthritis: An epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. *Arthritis & Rheumatology*, 20(1), 7-17. doi: 10.1002/art.1780200102.

[4] Burgdorfer, W. (1993). How the discovery of *Borrelia burgdorferi* came about. *Clinics in Dermatology*, 11(3), 335-338. doi: 10.1016/0738-081X(93)90087-S.

[5] Soroka, N.M., Nedosekov, V.V., Ovcharuk, N.P., Ovcharuk, V.M., & Kravchuk, O.O. (2020). Ixodes ticks – transmitters of dangerous transmissible infections and invasions agents. *Ukrainian Journal of Veterinary Sciences*, 11(3), 75-84. doi: 10.31548/ujvs2020.03.008.

[6] Klius, V.Yu. (2018). *Clinical and instrumental characteristics of chronic forms of Lyme disease with prevailing damage of the nervous system and improvement of their treatment tactics*. (Doctoral thesis, L.V. Hromashevskyi Institute of Epidemiology and Infectious Diseases of the NAMS of Ukraine, Kyiv, Ukraine).

[7] Ben, I.I. (2019). *Human granulocytic anaplasmosis: Clinical and epidemiological characteristics and diagnostic algorithm (on the example of Lviv and Volyn regions)*. (Doctoral thesis, Ivano-Frankivsk National Medical University of the Ministry of Health of Ukraine, Ivano-Frankivsk, Ukraine).

[8] Littman, M.P., Gerber, B., Goldstein, R.E., Labato, M.A., Michael, R., Lappin, M.R., & Moore, G.E. (2018). ACVIM consensus update on Lyme borreliosis in dogs and cats. *Journal of Veterinary Internal Medicine*, 32(3), 887-903. doi: 10.1111/jvim.15085.

[9] Barbour, A.G., & Gupta, R.S. (2021). The family *Borreliaceae* (Spirochaetales), a diverse group in two genera of tick-borne spirochetes of mammals, birds, and reptiles. *Journal of Medical Entomology*, 58(4), 1513-1524. doi: 10.1093/jme/tjab055.

[10] Bobe, J.R., Jutras, B.L., Horn, E.J., Embers, M.E., Bailey, A., Moritz, R.L., Zhang, Y., Soloski, M.J., Ostfeld, R.S., Marconi, R.T., Aucott, J., Ma'ayan, A., Keesing, F., Lewis, K., Ben Mamoun, C., Rebman, A.W., McClune, M.E., Breitschwerdt, E B., Reddy, P.J., Maggi, R., Yang, F., Neser,B., Ozcan, A., Garner, O., Di Carlo, D., Ballard, Z., Joung, H.A., Garcia-Romeu, A., Griffiths, R.R., Baumgarth, N., & Fallon, B.A. (2021). Recent progress in Lyme disease and remaining challenges. *Frontiers in Medicine*, 8, article number 666554. doi: 10.3389/fmed.2021.666554.

[11] Zhuang, X., Yang, X., Altieri, A.S., Nelson, D.C., & Pal, U. (2018). Borrelia burgdorferi surface located Lmp1 protein processed into region specific polypeptides that are critical for microbial persistence. *Cellular Microbiology*, 20(9), article number 12855. doi: 10.1111/cmi.12855.

[12] Bannwarth, A. (1941). Chronic lymphocytic meningitis, inflammatory polyneuritis and rheumatism. A contribution to the problem of allergy and the nervous system in two parts. *Arch Psychiatr Nervenkr*, 113, 284-376.

[13] Garin, Ch, & Bujadoux, A. (1993). Paralysis by ticks. *Clinical Infectious Diseases*, 16(1), 168-9. doi: 10.1093/clinids/16.1.168.

[14] Hellerström, S. (1951). Erythema chronicum migrans Afzelius with meningitis. *Southern Medical Journal*, 31(2), 34-227.

[15] Casselli, T., Divan, A., Vomhof-DeKrey, E.E., Tourand, Y., Pecoraro, H.L., & Brissette, C.A. (2021). A murine model of Lyme disease demonstrates that *Borrelia burgdorferi* colonizes the dura mater and induces inflammation in the central nervous system. *PLoS Pathogens*, 17(2), article number 1009256. doi: 10.1371/journal.ppat.1009256.

[16] Burgdorfer, W. (1993). The historical road to the discovery of *Borrelia burgdorferi*. In *Aspects of Lyme borreliosis* (pp. 21-28). Heidelberg: Springer. doi: 10.1007/978-3-642-77614-4_2.

[17] Lenhoff, C. (1948). Spirochetes in aetiologically obscure diseases. *Acta Dermato-Venereoloica*, 28, 295-324.

[18] Bäfverstedt, B. (1943). About benign cutis lymphadenosis. A clinical and pathological-anatomical. *Studie Acta. Dermatology Venerology*, 24, 1-102.

[19] Lipsker, D., & Jaulhac, B. (2009). Lyme Borreliosis. *Current Problems in Dermatology*, 37, 1-17. doi: 10.1159/000213066.

[20] Brunnemann, C. (2010). Investigations on the frequency of *Borrelia burgdorferi* sensu lato in *Ixodes ricinus* from East Western Pomerania. (Doctoral thesis, Ernst-Moritz-Arndt University of Greifswald, Leipzig, Germany).

[21] Hellerstrom, S., & Walter, B. (n.d.). Shelley papers. *Historical Medical Library of the College of Physicians of Philadelphia*. Retrieved from http://localhost:8081/repositories/2/archival_objects/24381.

[22] Binder, E., Doepfmen, R., & Hornstein, O. (1955). Transmission of erythema chronicum migrans from person to person in two passages Klin. *Wschr*, 33, 727-728.
[23] Götz, H. (1955). Acrodermatitis chronica atrophicans Herxheimer as an infectious disease. *Dermatologist*, 6, 249-252.
[24] Dammin, G.J. (1989). Erythema migrans: A chronicle. *Reviews of Infectious Diseases*, 11(1), 142-151. doi: 10.1093/clinids/11.1.142.
[25] Mast, W.E., & Burrows, W.M. (1976). Erythema chronicum migrans and "lyme arthritis". *JAMA*, 236(21), article number 2392. doi: 10.1001/jama.236.21.2392d.
[26] Burgdorfer, W. (1988). Ecological and epidemiological considerations of Rocky Mountain spotted fever. In D.H Walker (Ed.), *Biology of rickettsial diseases* (pp. 33-50). Boca Raton: CRC Press.
[27] Reik, L., Steere, A.C., Bartenhagen, N.H., Shope, R.E. & Malawista, S.E. (1979). Neurologic abnormalities of Lyme disease. *Medicine*, 58(4), 281-294.
[28] Apostolovic, D., Mihailovic, J., Commins, S.P., Hamsten, C., & van Hage,M. (2020). Allergenomics of the tick *Ixodes ricinus* reveals important α-Gal-carrying IgE-binding proteins in red meat allergy. *Allergy: European Journal of Allergy and Clinical Immunology*, 75(1), 217-220. doi: 10.1111/all.13978.
[29] Tretyakov, A.D. (1972). *Veterinary legislation*. Moscow: Kolos.
[30] Alwine, J.C., Reed, S.I., & Stark, G.R. (1977). Characterization of the autoregulation of simian virus 40 gene A. *Journal of Virology*, 24, 22-27. doi: 10.1128/Jvi.24.1.22-27.1977.
[31] Barbour, A.G., & Fish, D. (1993). The biological and social phenomenon of Lyme disease. *Science*, 260(5114), 1610-1616. doi: 10.1126/science.8503006.
[32] Preac-Mursic, V., Wilske, B., Gross, B., Weber, K., Pfister, H.W., Baumann, A., & Prokop, J. (1989). Survival of Borrelia burgdorferi in antibiotically treated patients with Lyme borreliosis. *Infection*, 17, 355-359. doi: 10.1007/BF01645543.
[33] Hyde, F.W., & Johnson, R.C. (1984). Genetic relationship of Lyme disease spirochetes to Borrelia, Treponema, and Leptospira. *Journal of Clinical Microbiology*, 20, 151-154.
[34] Lipschutz, B. (1913). Uber eine seltene Erythemform (Erythema chronicum migrans). *Arch Dermatol Syphil*, 118, 35-349.
[35] Thyresson, N. (1974). Acrodermatitis enteropathica. Report of a case healed with zinc therapy. *Acta Dermatology Venereology*, 54(5), 5-383.
[36] Weber, K., Burgdorfer, W., & Schierz, G. (1993). *Aspects of Lyme borreliosis*. Heidelberg: Springer.
[37] Southern, E.M. (1975). Detection of specific sequences among DNA fragments separated by gel electrophoresis. *Journal of Molecular Biology*, 98, 17-503. doi: 10.1016/S0022-2836(75)80083-0.
[38] Alwine, J.C., Kemp, D.J., & Stark, G.R. (1977). Method for detection of specific RNAs in agarose gels by transfer to diazobenzyloxymethyl-paper and hybridization with DNA probes. *Proceedings of the National Academy of Sciences of the United States of America*, 74, 5350-5354.
[39] Dammin, G.J. (1989). Erythema migrans: A chronicle. *Reviews of Infectious Diseases*, 11(1), 142-151. doi: 10.1093/clinids/11.1.142.
[40] Official website of the Lyme Disease Association. Retrieved from https://lymediseaseassociation.org/.
[41] Scientific Conferences. Lyme Disease Association. Retrieved from https://lymediseaseassociation.org/category/lda-conferences/summary-pages/.
[42] Lyme Disease Association. About the Lyme Disease Association. Retrieved from https://lymediseaseassociation.org/category/about-us/about-the-lyme-disease-association/.
[43] Lyme Disease Association Grant program. Retrieved from https://lymediseaseassociation.org/grants/outgoing/grants-2/.
[44] Official website of the European Commission. Retrieved from https://ec.europa.eu/.
[45] Horizon 2020. Retrieved from https://ec.europa.eu/search/?QueryText=Lyme+borreliosis+&op=Search&swlang=en&form_build_id=form-Kl-RfKBKbtYEbifrRBbnDrv4lRfLBQ_qNVDagnmUHM0&form_id=nexteuropa_europa_search_search_form.
[46] DualDur: A disruptive diagnostic technology that enables for the first time an early and accurate diagnosis of the tick-borne Lyme disease Retrieved from https://cordis.europa.eu/project/id/805609.
[47] Development of a prophylactic vaccine and diagnostic markers to prevent and diagnose Lyme borreliosis specific to Europe and North America. Retrieved from https://cordis.europa.eu/project/id/512598/it.
[48] A novel immunity-based test for early diagnosis of Lyme disease. Retrieved from https://cordis.europa.eu/project/id/720480.

[49] Highly sensitive and specific low-cost lab-on-a-chip system for Lyme disease diagnosis. (n.d.). Retrieved from https://cordis.europa.eu/project/id/262411/.
[50] Demonstration Activities for the clinical validation of the prototype HILYSENS Lab-on-a-Chip, 2014-2016. (n.d.). Retrieved from https://cordis.europa.eu/project/id/606348.
[51] Co-evolution and implications of vector adaptation: A case study on seabird ticks and Borrelia. (n.d.). Retrieved from https://cordis.europa.eu/project/id/221243.
[52] Effects of co-infections on the emergence of an avian disease Mycoplasma gallisepticum, 2018-2022. (n.d.). Retrieved from https://cordis.europa.eu/project/id/799609.
[53] Phylogeny of borrelia genus. (n.d.). Retrieved from https://cordis.europa.eu/project/id/FMBI960684.
[54] Co-evolution and implications of vector adaptation: A case study on seabird ticks and Borrelia. (n.d.). Retrieved from https://cordis.europa.eu/project/id/221243.
[55] Development of a prophylactic vaccine and diagnostic markers to prevent and diagnose Lyme borreliosis specific to Europe and North America. (n.d.). Retrieved from https://cordis.europa.eu/project/id/512598/reporting.
[56] A functional genomics study of lysyl-trna synthesis as a target for the diagnosis and treatment of microbial infections and mitochondrial myopathies. (n.d.). Retrieved from https://cordis.europa.eu/project/id/QLG2-CT-1999-00660.
[57] Anti-tick vaccines to prevent tick-borne diseases in Europe. (n.d.). Retrieved from https://cordis.europa.eu/project/id/602272.
[58] Lyme borreliosis in North Africa: Risk assessment and implications for tick management and for control of the human disease. (n.d.). Retrieved from https://cordis.europa.eu/project/id/ICA3-CT-2000-30009/de.
[59] Complexity and predictability of epidemics: Toward a computational infrastructure for epidemic forecasts. (n.d.). Retrieved from https://cordis.europa.eu/project/id/204863.
[60] A novel immunity-based test for early diagnosis of Lyme disease. (n.d.). Retrieved from https://cordis.europa.eu/project/id/720480.
[61] Apostolovic, D., Mihailovic, J., Commins, S.P., Wijnveld, M., Kazimirova, M., Starkhammar, M., Stockinger, H., Platts-Mills, T.A., Velickovic, T., Hamsten, C., van Hage, M. (2020). Allergenomics of the tick *Ixodes ricinus* reveals important α-Gal-carrying IgE-binding proteins in red meat allergy. *Allergy*, 75(1), 217-220. doi: 10.1111/all.13978.
[62] Szymczak, Z., Płusa, T., Baranowski, P., & Krawczyk, J. (2021). Hip arthoplasty in a forester after numerous tick bites. *International Journal of Occupational Medicine and Environmental Health*, 34(5), 693-699. doi: 10.13075/ijomeh.1896.01697.
[63] Winslow, C., & Coburn, J. (2019). Recent discoveries and advancements in research on the Lyme disease spirochete *Borrelia burgdorferi*. *F1000Research*, 8, article number 763 doi: 10.12688/f1000research.18379.1.
[64] Horizon Europe. (n.d.). Retrieved from https://ec.europa.eu/info/research-and-innovation/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe_en.
[65] Casselli, T., Divan, A., Vomhof-DeKrey, E.E., Tourand, Y., Pecoraro, H.L., & Brissette, C.A. (2021). A murine model of Lyme disease demonstrates that *Borrelia burgdorferi* colonizes the dura mater and induces inflammation in the central nervous system. *PLoS Pathogens*, 17(2), article number 1009256. doi: 10.1371/journal.ppat.1009256.
[66] Order of the Ministry of Health of Ukraine No. 218 "On Strengthening the Measures of Diagnosis and Prevention of Ixodid Tick-Borne Borreliosis in Ukraine". (2005, March). Retrieved from https://zakon.rada.gov.ua/rada/show/v0218282-05#Text.
[67] Research Institute of Epidemiology and Hygiene. (n.d.). Retrieved from https://new.meduniv.lviv.ua/en/pidrozdily/naukovo-doslidnyj-instytut-epidemiologiyi-ta-gigiyeny/.
[68] Berezovsky, A.V. (2007). *Modern preparations of pharmacological correction and chemoprophylaxis of animals*. Kyiv: Vetinform.
[69] Stiasny, K., Santonja, I., Holzmann, H., Essl, A., Stanek, G., Kundi, M., & Heinz, F.X. (2005). The regional decline and rise of tick-borne encephalitis incidence do not correlate with Lyme borreliosis, Austria, 2005 to 2018. *Eurosurveillance*, 26(35), article number 2002108. doi: 10.2807/1560-7917.es.2021.26.35.2002108.
[70] Galat, V.F., Berezovskyi, A.V., Prus, M.P., & Soroka, N.M. (2003). *Parasitology and invasive diseases of animals*. Kyiv: Higher Education.
[71] Reik, Jr.L., Burgdorfer, W., & Donaldson, J.O. (1986). Neurologic abnormalities in Lyme disease without erythema chronicum migrans. *The American Journal of Medicine*, 81(1), 73-78. doi: 10.1016/0002-9343(86)90185-3.

Історія відкриття та досліджень Лайм-бореліозу в тварини і людини

Наталія Михайлівна Сорока, Оксана Олексіївна Кравчук, Олена Василівна Журенко

Національний університет біоресурсів і природокористування України
03041, вул. Героїв Оборони, 15, м. Київ, Україна

Анотація. Актуальність статті зумовлена суттєвим значенням історії відкриття та досліджень Лайм-бореліозу для медичної науки і, зокрема, ветеринарної медицини, оскільки на дослідженнях учених, які довели існування цієї хвороби у тварин і людини, будуються нові теорії, експерименти, висновки, накопичується позитивний досвід щодо методів і схем лікування та профілактики. Метою дослідження був аналіз літературних першоджерел із висвітлення історії відкриття, результатів дослідження хвороби Лайм-бореліозу для розуміння особливостей її перебігу та пошуку ефективних методів діагностики та засобів лікування. Узагальнено хронологію основних результатів, що підтверджують існування Лайм-бореліозу, спричиненого іксодовими кліщами. Проаналізовано наукові джерела з висвітлення історії відкриття та досліджень Лайм-бореліозу для розуміння особливостей її перебігу та пошуку ефективних методів лабораторної діагностики та засобів лікування. Визначено основні проєкти програми Європейського Союзу, які спрямовані на фінансування досліджень та інноваційних розробок «Горизонт 2020». З'ясовано, що проєкти з напряму дослідження Лайм-бореліозу також стосуються певних тем, зокрема, створення тестів для виявлення хвороби Лайма, дослідження переносників збудників цієї хвороби, розроблення відповідної вакцини, оцінювання ризиків наслідків щодо здоров'я людини та тварин. Зроблені висновки, що основними напрямами роботи є: стійкість хвороб і їхніх збудників, які передаються іксодовими кліщами; природний контроль іксодових кліщів; виявлення патогенних збудників в іксодових кліщах; рівень зараження хребетних тварин; ареали та природні вогнища переносників і їх хазяїв; тестування та лікувальні випробування; вплив магнітного поля на борелій; картографування геному видів Borrelia, візуалізація мозку людини за дослідження хвороби; дослідження за полімеразною ланцюговою реакцією; ендокринні дослідження; імунні комплекси, діагностика нейропсихіатричних ускладнень у дітей і дорослих. Практична цінність наукового дослідження полягає у поінформованості сучасних науковців щодо хронології вивчення захворювання на Лайм-бореліоз, основних шляхів розповсюдження і методів його діагностики у тварини і людини, визначення перспектив подальших досліджень згідно з висвітленими у статті актуальними проблемами, що вирішуються у межах міжнародних проєктів

Ключові слова: іксодові кліщі, борелії, спірохети, укуси іксодових кліщів