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Lyme disease – clinical course features (literature overview)

Relevance. Infectious diseases have always been and remain relevant throughout the history of mankind. In particular, in recent years, the number of cases of zoonotic anthropogenic diseases, the pathogens of which are transmitted mainly through tick bites, has increased. The epidemiological situation with regard to such infections as Lyme borreliosis and tick-borne encephalitis changes every year. With the growing popularity of tourism, these infections are becoming a problem outside of endemic regions. An increasing number of cases of these diseases unrelated to occupational risk factors are being registered, which attracts attention and requires a review of attitudes towards these diseases, deeper research and study of their pathogenesis, clinical manifestations, diagnostic and treatment methods, as well as the search for and application of the most effective prevention methods.

The main goal of the study: is to depict both typical and atypical clinical features of Lyme's disease, while briefly mentioning its' prevention measures, diagnosis and treatment, using a variety of recently published literature.

Materials and methods: the article uses the bibliographic method and is a review of existing works on PubMed and Google Scholar, as well as other on-topic literature.

Research results and their discussion: analysed information from modern foreign and domestic sources. The data obtained indicate the relevance of the chosen topic. Due to the fact that in Ukraine in recent years less attention has been paid to pest control, due to insufficient funding for this sector and attempts to eliminate the sanitary and epidemiological link, the amount of insects carrying the pathogens of the above diseases is growing year by year. City parks and some courtyards adjacent to houses are dangerous to visit. This problem becomes especially acute from May to October every year. An analysis of foreign sources has shown a significant spread of Lyme borreliosis in economically developed countries, namely Switzerland, Italy, Germany, and the Czech Republic. Of course, this is due to the complexity of disinfection and the lack of government programmes for insect extermination.

Conclusions: So, the imperfection of the preventive link, namely sanitary and educational measures, the severity of these diseases, complications both after the diseases and after their treatment. All this prompts us to look for ways to solve these problems in order to prevent the emergence of new cases and improve treatment measures.

Key words: ticks, Lyme disease, specific prophylaxis.

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Хвороба Лайма – особливості клінічного перебігу (огляд літератури)

Актуальність. Інфекційні захворювання завжди були і залишаються актуальними протягом усієї історії людства. Зокрема, останніми роками збільшилася кількість випадків зоонозних антропогенних захворювань, збудники яких передаються переважно через укуси кліщів. Епідеміологічна ситуація щодо таких інфекцій, як Лайм-бореліоз та кліщовий енцефаліт, змінюється шороку. З ростом популярності туризму ці інфекції стають проблемою поза межами ендемічних регіонів. Зростає кількість випадків цих захворювань, які не пов'язані з професійними факторами ризику, що привертає увагу та вимагає перегляду підходів до цих захворювань, глибшого дослідження їх патогенезу, клінічних проявів, методів діагностики та лікування, а також пошуку та застосування найефективніших методів профілактики.

Основна мета: Основна мета дослідження – описати як типові, так і нетипові клінічні ознаки хвороби Лайма, коротко згадуючи заходи профілактики, діагностики та лікування, використовуючи різноманітну нещодавно опубліковану літературу.

Матеріали та методи: Стаття використовує бібліографічний метод та є оглядом існуючих робіт у PubMed та Google Scholar, а також іншої літератури за темою.

Результати дослідження та їх обговорення: Проаналізували інформацію із сучасних закордонних та вітчизняних джерел. Отримані дані свідчать про актуальність обраної теми.

У зв'язку з тим, що останніми роками в Україні боротьбі зі шкідниками приділяється менше уваги, через недостатнє фінансування цієї галузі та намагання ліквідувати санітарно-епідеміологічний зв'язок, кількість комах-переносників збудників вищевказаних хвороб з кожним роком зростає. Міські парки та деякі прибудинкові двори небезпечні для відвідування. Ця проблема стає особливою гострою з травня по жовтень кожного року.

Аналіз зарубіжних джерел показав значне поширення Лайм-бореліозу в економічно розвинених країнах, а саме Швейцарії, Італії, Німеччині, Чехії. Звичайно, це пов'язано зі складністю дезінсекції та відсутністю державних програм знищення комах.

Висновки: Отже, недосконалість профілактичної ланки, а саме санітарно-просвітницьких заходів, тяжкість цих захворювань, ускладнення як після перенесених захворювань, так і після їх лікування. Усе це спонукає нас шукати шляхи вирішення цих проблем, щоб запобігти виникненню нових випадків та покращити заходи лікування.

Ключові слова: кліщі, хвороба Лайма, специфічна профілактика.

Introduction. Lyme borreliosis is a tick-borne disease that occurs primarily in temperate regions of the northern hemisphere and is caused by the bacterium *Borrelia burgdorferi* in North America and *Borrelia afzelii* or *Borrelia garinii* in Europe and Asia [1].

The infection usually begins with a skin lesion known as erythema migrans (stage I), which, if left untreated, can be followed by early infection, including neurological abnormalities (stage II), and late infection, especially arthritis or chronic atrophic acrodermatitis (stage III). During an infection, bacteria migrate through the host's tissues, adhere to certain cells and can escape immune recognition and destruction. However, these organisms eventually become the target of immune reactions and most of the inflammatory manifestations of the infection are eliminated [2; 3].

With the exception of patients with erythema migrans, the diagnosis of Lyme borreliosis is based on a characteristic clinical presentation of signs and symptoms with serological infection confirmation. All manifestations of the infection can usually be treated with an appropriate antibiotic regimen, but in some patients the disease may be accompanied by post-infectious consequences. Prevention of lyme borreliosis is primarily based on avoiding tick bites by wearing personal protective equipment [4; 5].

Lyme borreliosis. Tick-borne borreliosis (Lyme disease, systemic tick-borne borreliosis, Lyme borreliosis) is an infectious neurotropic disease, the causative agent of which is also transmitted by the above-mentioned tick species [6]. The bacterium *Borrelia burgdorferi*, which belongs to the class of spirochetes, was first described in 1975, and the disease it causes was named after the endemic region – the town of Lyme in Connecticut – Lyme borreliosis [7; 8].

Wei-Gang Qiu and Che L. Martin cite 28 known strains of *Borrelia burgdorferi*, although some researchers suggest that there are many undiscovered strains today. To date, 12543 genes have been identified, making *Borrelia burgdorferi* one of the most complex bacteria with one of the most complex genomes.

Presumably due to close coexistence with mammals and ticks, in which they have always played the role of host, *Borrelia burgdorferi* has lost the ability to synthesise nucleotides, amino acids and fatty acids. *Borrelia burgdorferi* has a constant need to adapt its nutrient acquisition mechanism due to the alternation of its presence in the body of tick and mammalian hosts. The host's defence is often based on the sequestration of essential nutrients for cellular life processes, which is caused by the presence of iron ions [9]. However, in the course of its evolution, *Borrelia burgdorferi* has acquired the ability to maintain its own metabolism with the help of magnesium and zinc ions. The ability of *Borrelia burgdorferi* to «evade the immune response» of the host organism has also been documented through non-reciprocal homologous recombination, which results in the creation of a non-repeating amino acid sequence – this allows the bacterium to remain «undetected» by the immune system of the mammal in which it parasitises [10; 11].

Clinical course features. Lyme borreliosis. The clinical course of Lyme disease is varied and occurs in three stages. Spontaneous recovery may occur at any stage, and there may be no clear transition between stages. The main pathogenetic mechanism is pericapillary lymphocytic inflammation, which explains the presence of a clear erythema on the skin. Since the entire pathophysiological process of inflammation occurs in the lumen of the

capillary, it is likely to cause thrombosis of these vessels, which in turn leads to severe neurological deficits: from facial paresis to paraplegia. This pathogenetic model can also explain why it is not always possible to detect changes in the cerebrospinal fluid in neuroborreliosis – *Borrelia* does not need to penetrate the blood-brain barrier to cause the relevant symptoms. Inflammation in the tissues of the joints, heart or kidneys are other examples of the same pathogenetic principle [12; 13; 14].

In addition, Lyme borrelia also appear to have an affinity for connective tissue collagen, which is clinically manifested by myositis or fibromyalgia. When a tick bite falls on areas with loose connective tissue, such as the earlobes or nipples, it results in a reddish lipomatous swelling – lymphadenosis cutis benigna Bäfverstedt (*Borrelia* lymphocytoma).

Stage I: the typical manifestation is erythema migrans. A few days or weeks after a tick bite, a papule appears at the bite site, which rapidly grows to the size of an erythema. It is bordered by sharp edges and often has a lumen in the centre.

Stage II: the main symptom of stage II is Garin Bujadu-Bannwarth meningopolyneuritis. After a tick bite, a burning sensation occurs within a few weeks or months. During the initial stage, the pain syndrome is asymmetrical in more than 90% of cases. There is an unsystematic widespread flaccid paralysis. The neurological deficit affects the cranial nerves in approximately 60% of cases, mainly in the form of unilateral or bilateral facial nerve palsy [15; 16].

Heart damage is manifested by myocarditis, pericarditis or pancreatitis. ST-segment changes, atrial fibrillation, ventricular extrasystoles, tachycardia, possibly cardiomegaly, left ventricular dysfunction, severe heart failure, and syncope are common [17].

A rare cutaneous manifestation is benign Bäfverstedt's lymphadenosis of the skin (*Borrelia* lymphocytoma) [18].

Stage III: Lyme arthritis and Herxheimer's chronic atrophic acrodermatitis are manifestations of this stage. They occur months or years after the bite. Lyme arthritis can be recurrent or chronic, mono- or oligoarticular. The knee joints are most often affected, as well as the joints of the elbows, fingers, legs, wrist joints, temporomandibular joints. Herxheimer's chronic atrophic acrodermatitis is characterised by an initial infiltrative stage that progresses to skin atrophy (thin cigarette paper), and later the skin becomes pale. Changes occur mainly on the extensor surface of the limbs. [19; 20; 21].

Diagnosis and treatment. When diagnosing Lyme disease, it is necessary to establish whether the patient has been in endemic areas.

In India, a case of Lyme disease with typical and atypical symptoms was reported in 2016. The patient, a 10-year-old boy, a resident of a village located in a hilly area, was admitted to the hospital with complaints of a large brownish spot with a red rim around it, which was rapidly increasing in size. The child had no manifestations of fever or any other systemic reactions. According to the patient, a few days before the onset of symptoms, he had gone to the local forest. The examination revealed an erythematous ring-shaped plaque on the posterior surface of the left tibia measuring 6 × 5 cm. There was a fluid-filled

blister in the middle of the plaque. In addition, indurative edema was noted around the lesion, as well as tenderness and local lymphadenopathy. There were petechiae in the scapular area, and several maculopapular elements on the dorsal surfaces of the hands and lower legs. No pathological changes were found in the peripheral blood smear. Serology for *Borrelia burgdorferi* Ospc antigen (23 kDa) was performed by enzyme-linked immunosorbent assay. IgM was elevated by 4.4 U/ml (normal <0.90), while IgG was within normal limits (0.3 U/ml (normal <0.90)), indicating an acute infection. Western blot could not be performed for financial reasons. The biopsy of the lesion margin showed a moderate perivascular lymphocytic infiltrate with a focus of spongiosis, papillary dermis and extravasation of erythrocytes [22].

Treatment was started immediately with doxycycline 100 mg tablets twice daily along with other symptomatic therapy. After 2 weeks, there was a marked improvement, which was partly due to skin detachment. The medication was continued for 3 weeks, which led to clinical resolution of the erythema [23].

Specific prophylaxis measures. Given the difficulties that can arise in the treatment of Lyme disease and the emergence of possible complications that significantly worsen the prognosis of the disease, there is a need to develop effective methods of preventing these diseases.

As for specific methods of preventing Lyme disease, there is currently no single vaccine that can prevent the progression of this disease after an infected tick bite [24].

Currently, research is being conducted by Valneva SE and Pfizer, which are jointly developing a candidate vaccine, VLA15. This is a polyvalent protein vaccine containing recombinantly produced OspA proteins from six *Borrelia* serotypes as an antigen. These antigens are fixed on the outer membrane of the bacteria [24].

The candidate vaccine is currently being tested in two Phase II trials (VLA15-201 and VLA15-202). The first results have already been published in the company's press releases.

In the VLA15-202 study, 246 healthy adults aged 18 to 65 were randomised in a 2:2:1 ratio. In two groups, serum subjects received a low and a higher dose of the vaccine with the Al(OH)₃ adjuvant. The third group received a placebo vaccine. The vaccine was administered intramuscularly on days 1, 57, and 180.

As of now, the authors consider the study almost complete. This is evidenced by the antibody response one month after the completion of the primary immunisation in all dose groups and for all serotypes. As antibody titres declined over time in all groups but remained above baseline, it was concluded that a booster strategy would be necessary. To this end, participants who had completed the full course of primary vaccination with 180 mcg of VLA15 were invited to continue the study in the booster phase. For this purpose, 39 participants received an additional dose of 180 mcg of VLA15 18 months after the initial immunisation. 19 people received a placebo vaccination.

VLA15 was safe and well tolerated at all doses and age groups tested. [25].

The study builds on previous positive phase II studies that also included children. In total, there is data on 800 participants aged 5 to 65 years. A third phase of the study is planned for next year.

Conclusions. We analysed information from modern foreign and domestic sources. The data obtained indicate the relevance of the chosen topic.

1. Due to the fact that in Ukraine in recent years less attention has been paid to pest control, due to insufficient funding for this sector and attempts to eliminate the sanitary and epidemiological link, the amount of insects carrying the pathogens of the above diseases is growing year by year. City parks and some courtyards adjacent to houses are dangerous to visit. This problem becomes especially acute from May to October every year.

2. The role of family medicine is growing, when family doctors conduct health education work to inform the population about the severity of these diseases, ways of their transmission and possible foci of infection. Children are at risk because they pay insufficient attention to this information and spend most of their

leisure time in places of possible infection (forests, parks, playgrounds, etc.).

3. An analysis of foreign sources has shown a significant spread of Lyme borreliosis in economically developed countries, namely Switzerland, Italy, Germany, and the Czech Republic. Of course, this is due to the complexity of disinfection and the lack of government programmes for insect extermination.

4. According to the literature, the disease in children is milder, and there are even cases of rapid resolution of the disease. However, treatment is usually associated with the use of tetracycline antibiotics, which in adults and especially in children affect the bone system, which is dangerous given the linear bone growth.

5. All of the above points to the imperfection of the preventive link – namely, sanitary and educational activities, the severity of these diseases, and complications both after the disease and after their treatment. All of this prompts us to look for ways to solve these problems in order to prevent the emergence of new cases and improve treatment measures.

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Personal contribution of the author:

Moskaliuk V.D. – idea, purpose, study design, manuscript preparation, literature search, funds collection;

Balaniuk I.V. – idea, purpose, data interpretation, manuscript preparation, literature search;

Melenko S.R. – idea, study design, data interpretation, literature search;

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