

Clinical-epidemiologic and serologic characteristics of Lyme disease in the Zaporizhzhia region (a retrospective analysis for 2015–2019 according to the Municipal Institution “Regional Infectious Hospital” of Zaporizhzhia Regional Council)

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The aim of the work is to clarify the clinical and laboratory features of Lyme disease in the Zaporizhzhia region on the basis of a retrospective clinical, epidemiological and serological analysis of this disease cases in the period from 2015 to 2019.

Materials and methods. A retrospective analysis of 62 medical cards of stationary patients with Lyme disease for the period from 2015 to 2019 was carried out. The age of the patients ranged from 18 to 79 years. There were 38 men and 24 women. All the patients were given a traditional complex clinical-laboratory examination; ELISA was used to defined serum IgM and IgG to *Borrelia burgdorferi*.

Results. According to the study results it was found that Lyme disease in the Zaporizhzhia region had a clear seasonal prevalence in summer (56.5 %) and spring (25.8 %). The vast majority of patients (80.6 %) clearly indicated the tick bite. The disease was mostly acute (90.3 %) with a predominance of erythema (94.6 %). In the acute course of the disease, patients were seropositive in 75.0 % of cases with simultaneous detection of both IgM and IgG to *Borrelia burgdorferi*, and positive IgM in the absence of IgG. Seronegative 25.0 % of patients required clear clinical and epidemiological data to confirm the diagnosis. Under prolonged and chronic conditions, patients had positive IgG to *Borrelia burgdorferi* (100 %) and IgM (50.0 %).

Certain clinical and laboratory features at different course of Lyme disease were revealed. So, the acute course was characterized by the predominance of erythema (94.6 %), mild or no manifestations of general intoxication syndrome, lack of pathological changes in the hemogram in most patients (80.4 %). In the prolonged and chronic course, there was no history of erythema, clinical symptoms were polymorphic, half of the patients had increased erythrocyte sedimentation rate in the absence of changes in blood count, mild cytolytic syndrome and hyperbilirubinemia.

Conclusions. As a result of the retrospective analysis of Lyme disease cases in the period from 2015 to 2019, certain patterns of epidemiological, clinical and serological changes in different courses of this infection in the Zaporizhzhia region were revealed, namely the clear seasonality of the disease, in the acute course – the predominance of erythema and different variants of serological profile in patients, and in prolonged and chronic course – polymorphism of all clinical symptoms and no history of erythema.

Ключові слова:

хвороба Лайма, клініка, серологічна діагностика.

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Клініко-епідеміологічна та серологічна характеристика хвороби Лайма в Запорізькій області (ретроспективний аналіз за 2015–2019 рр. за даними КУ «Обласна інфекційна лікарня» ЗОР)

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Мета роботи – з'ясування клініко-лабораторних особливостей перебігу хвороби Лайма у Запорізькому регіоні на підставі ретроспективного клініко-епідеміологічного та серологічного аналізу випадків цього захворювання в області в період з 2015 до 2019 року.

Матеріали та методи. Здійснили ретроспективний аналіз 62 медичних карт стаціонарних пацієнтів із хворобою Лайма за період 2015–2019 рр. Вік хворих – від 18 до 79 років, 38 чоловіків, 24 жінки. Усім хворим здійснили традиційне комплексне клініко-лабораторне обстеження, методом імуноферментного аналізу в крові визначили IgM та IgG до *Borrelia burgdorferi*.

Результати. У результаті дослідження встановили: хвороба Лайма в Запорізькій області мала чітку сезонність із переважанням кількості хворих влітку (56,5 %) та навесні (25,8 %). У переважній більшості хворих (80,6 %) достеменно відомо про укуси кліща. Захворювання здебільшого (90,3 %) мало гострий перебіг із переважанням еритемної форми (94,6 %). За умов гострого перебігу хвороби пацієнти були серопозитивними у 75,0 % випадків з одночасним виявленням IgM та IgG до *Borrelia burgdorferi*, а також позитивними за IgM без виявлення IgG. Серонегативність 25,0 % хворих спричинила необхідність чітких клініко-епідеміологічних даних для підтвердження діагнозу. Якщо перебіг хвороби тривалий і хронічний, пацієнти мали позитивні IgG до *Borrelia burgdorferi* (100 %) та IgM (50,0 %).

Визначили клініко-лабораторні особливості перебігу хвороби Лайма. Так, гострий перебіг характеризувався переважанням еритемної форми (94,6 %), ознаки загальної інтоксикаційного синдрому виражені слабо чи взагалі не виявлені, патологічних змін у гемограмі у більшості пацієнтів (80,4 %) не було. У разі тривалого та хронічного перебігу не було даних анамнезу щодо

наявності еритеми, клінічна симптоматика поліморфна, у половини пацієнтів визначили підвищення швидкості осідання еритроцитів без змін формули крові, слабо виражені цитолітичний синдром і гіпербілірубінемія.

Висновки. Одержані під час ретроспективного аналізу випадків хвороби Лайма за 2015–2019 рр. результати дали змогу встановити закономірності епідеміологічних, клінічних і серологічних змін, що спричинені цією інфекцією, в пацієнтів у Запорізькій області: чітка сезонність хвороби; при гострому перебігу – перевалювання еритемної форми та різні варіанти серологічного профілю хворих; при тривалому та хронічному – поліморфність клінічної симптоматики, серопозитивність у всіх випадках, випадки еритеми в анамнезі не зафіксовані.

Lyme disease is a naturally occurring bacterial zoonotic infectious disease caused by various genes of the *Borrelia* complex, characterized by predominant skin lesions in the form of erythema and a tendency to chronicity of the process with damage to the nervous and musculoskeletal systems. Lyme disease remains one of the most common transmissible tick-borne infections in the Northern Hemisphere, with the most common vector being *Ixodes* spp. [1,2].

The morbidity of Lyme disease in the world has been growing steadily over the past two decades [3]. According to the Centers for Disease Control and Prevention (CDC), about 300.000 cases are reported annually in the United States [4]. In the European region, the highest incidence is recorded in Central and Northern Europe, as well as in the Baltic countries [3,5]. In Ukraine, in 2019, 4482 cases were registered [6]; in 2019, the overall incidence in the Zaporizhzhia region was 2.25 Lyme disease cases per 100.000 population [7]. Climate change, the transfer of natural ecosystems to cities or recreational areas as a result of urbanization lead to the expansion of both the source and vector of Lyme disease, which is likely to cause an even greater increase in this infection incidence rate [8].

Clinical diagnosis of Lyme disease has significant difficulties due to the polymorphic clinical manifestations of the disease, which in turn depends on the characteristics of a causative pathogen, and the clinical form and stage of the disease. It is known that the causative agent of Lyme disease is often one of three genes: *Borrelia burgdorferi sensu stricto*, *B. afzelii* and *B. garinii* [9,10]. However, other genes, such as *B. bissettae*, *B. lusitanae*, *B. spielmanii*, and *B. valaisiana*, have recently been reported, mainly in Europe [11]. The geographical distribution and heterogeneity of the pathogen determine a certain difference in clinical manifestations due to the specificity of the pathogen by the source of infection and tropism to target organs. *Borrelia burgdorferi sensu stricto* is distributed mainly in North America and is associated with arthritis and neuroborreliosis [12]. *B. afzelii*, *B. garinii*, *B. burgdorferi*, *B. spielmanii* and *B. bavariensis* are common in Asia and Europe [13], neuroborreliosis is associated with *B. garinii*, and chronic skin lesions, including chronic acrodermatitis attributed to *B. afzelii* [10].

In addition, polymorphic clinical manifestations of Lyme disease depend not only on the heterogeneity of the pathogen, but also on the stage of the process. The early localized stage is characterized by the presence of migrating erythema in the site of a tick bite; however, erythema is absent in at least 20 % of cases [14]. Therefore, even the general intoxication syndrome, which occurs at this stage in some patients, in the absence of erythema or in the presence of non-standard clinical variations, leads to diagnostic errors [15,16].

If Lyme disease is not diagnosed at an early stage, the pathogen is disseminated early hematogenously

or lymphogenously with the involvement of various target organs in the pathological process. Therefore, in addition to general intoxication, patients develop various multisystem lesions, such as multifocal migratory erythema, benign lymphocytoma of the skin, meningitis, encephalitis, polyradiculoneuropathy, neuritis or facial nerve neuropathy, carditis. Further progression of Lyme disease is characterized by the formation of late disseminated stage, which is most often clinically manifested by progression of neurological disorders, chronic atrophic skin lesions, large joint oligoarthritis due to autoimmune and immunopathological reactions [17,18]. All this further complicates not only the diagnosis of this disease, but also significantly reduces the effectiveness of etiotropic treatment.

Therefore, the above necessitates the analysis of clinical, epidemiological and laboratory features of Lyme disease in the Zaporizhzhia region, that would determine certain patterns of this infection and improve early diagnosis.

Aim

The aim of the work is to clarify the clinical and laboratory features of Lyme disease in the Zaporizhzhia region on the basis of a retrospective clinical, epidemiological and serological analysis of this disease cases in the period from 2015 to 2019.

Materials and methods

A retrospective analysis of 62 medical records of inpatients with Lyme disease (A 69.2), who were examined and treated in the departments of the Municipal Institution “Regional Infectious Diseases Clinical Hospital” of the Zaporizhzhia Regional Council for the period from 2015 to 2019. The age of patients ranged from 18 to 79 years, the mean age was 46.1 ± 2.2 years. There were 38 men and 24 women.

All the patients with Lyme disease underwent a traditional comprehensive clinical and laboratory examination at the hospital, and ELISA were performed to determine serum IgM and IgG to *Borrelia burgdorferi*. The course of Lyme disease was evaluated according to the recommendation [19], based on which the early period (including stages of local infection and dissemination) and the late period (stage of persistent infection) was defined. Depending on the nature of the course, there were acute course (up to 3 months), subacute course (up to 6 months) and chronic (prolonged or recurrent) course.

Statistical data processing was performed using the program Statistica 13 for Windows (StatSoft Inc., No. JPZ8041382130ARCN10-J).

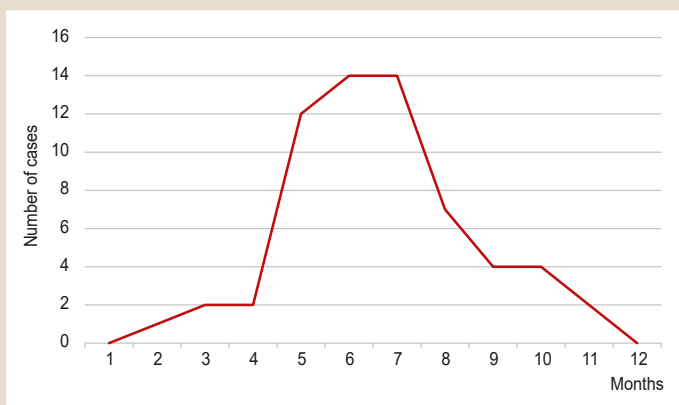


Fig. 1. Dynamics of the number of patients with Lyme disease in different months of the year according to the retrospective analysis.

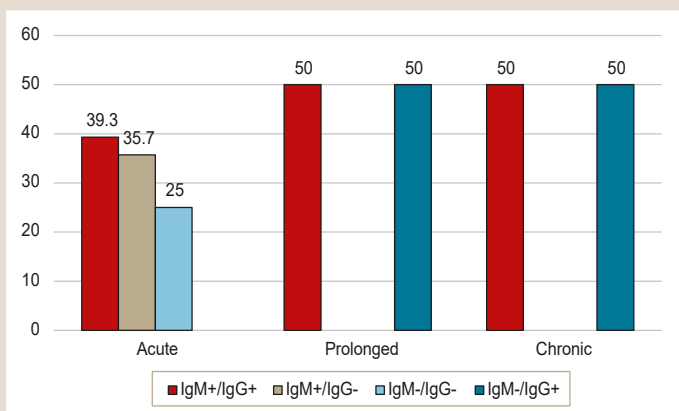


Fig. 2. Serological profile of IgM and IgG to *Borrelia burgdorferi* in patients with different clinical course of Lyme disease.

Results

According to the results of the epidemiological anamnesis, it was found that Lyme disease in the Zaporizhzhia region has a clear seasonality with a predominance of patients in summer ($n = 35$, 56.5 %) and spring ($n = 16$, 25.8 %). It should be noted that in autumn, the number of patients decreased rapidly ($n = 10$, 16.1 %), and in winter, there were only 1 (1.6 %) case of this infection during the entire observation period (Fig. 1).

The vast majority of patients ($n = 50$, 80.6 %) in the epidemiological history clearly indicated the tick bite when visiting various natural sites. It is worth noting that none of persons sought medical help after the tick bite and, accordingly, they did not receive urgent post-exposure prophylaxis.

Analysis of the clinical course showed that Lyme disease was mostly acute ($n = 56$, 90.3 %), in some cases prolonged ($n = 2$, 3.2 %) and chronic ($n = 4$, 6.5 %). The disease mainly was moderate ($n = 53$, 85.5 %), 9 (14.5 %) patients had a mild course, patients with severe Lyme disease during the study period was not detected.

The analysis of serological tests for IgM and IgG to *Borrelia burgdorferi* showed that all patients with prolonged (>3 months) and chronic (>6 months) Lyme disease were seropositive for IgG to *Borrelia burgdorferi*, and every second patient was positive for both IgM and IgG. However,

patients with acute Lyme disease who were examined on average on day 23.7 ± 2.3 of the disease demonstrated certain features of the serological profile in the study of different classes of antibodies to *Borrelia burgdorferi*. During this period of examination, 75.0 % (42 of 56) patients with acute disease were seropositive, patients with positive both IgM and IgG to *Borrelia burgdorferi* ($n = 22$, 39.3 %) were detected with the same frequency, and patients with positive IgM to *Borrelia burgdorferi* in the absence of IgG to the pathogen accounted for 35.7 % ($n = 20$). Seronegative was one of the four patients ($n = 14$, 25.0 %) with acute Lyme disease (Fig. 2). Therefore, it should be noted that the basis for confirmation of the diagnosis in these cases were clinical and epidemiological data, namely epidemiological history of tick bite a few days or weeks before the onset of clinical manifestations, in addition, erythema was diagnosed in all these patients with Lyme disease.

In the analysis of clinical variants of acute Lyme disease, a clear prevalence of erythema was detected – in 94.6 % (53 of 56) of patients, and in 5.7 % (3 of 53) of cases, the presence of erythema was combined with joint damage. In patients with erythema, lesions were most commonly localized on the skin of the lower ($n = 29$, 54.7 %) and upper extremities ($n = 9$, 17.0 %), less often – on the skin of the trunk, namely on the skin of the anterior surface of the chest ($n = 6$, 11.3 %) and the anterior abdominal wall ($n = 5$, 9.4 %), lumbar skin ($n = 2$, 3.8 %), scrotal skin ($n = 1$, 1.9 %), and the presence of erythema was recorded on the skin around the ear in 1 (1.9 %) case. The size of the formed erythema varied in a wide range with a diameter from 2.5 cm in the formation of annular erythema to 40 cm in cutaneous manifestations in the form of migrating erythema. At the same time, 17.0 % (9 of 53) of patients with erythema experienced moderate itching of the skin at the site of erythema. It was noteworthy that in patients with erythematous Lyme disease, signs of general intoxication syndrome were either absent or manifested in some patients by short-term subfebrile temperature ($n = 3$, 5.7 %) and moderate weakness ($n = 5$, 9.4 %).

In the acute course of the disease, the erythema-free form was recorded in 5.4 % (3 of 56) of patients. The development of this form was accompanied by the appearance of moderate general intoxication syndrome due to subfebrile temperature, astheno-vegetative manifestations, and one case was accompanied by damage to the joints and central nervous system in the form of serous meningitis. Given the absence of erythema characteristic of this infection in all patients with erythematous form, the diagnosis of Lyme disease was serologically confirmed by the detection of IgM and IgG to *Borrelia burgdorferi* during a comprehensive diagnostic examination. It is also noteworthy that patients with acute Lyme disease, despite the prevalence of erythema, were hospitalized in the third week after the onset of clinical manifestations.

Analysis of general clinical data from laboratory studies in patients with acute Lyme disease showed that most patients ($n = 45$, 80.4 %) had no pathological changes in the hemogram. However, in 7 (12.5 %) patients, leukopenia was found from $3.7 \times 10^9/l$ to $2.0 \times 10^9/l$, averaging up to $(2.96 \pm 0.29) \times 10^9/l$, in 4 (7.1 %) patients, on the contrary, leukocytosis ranged from $9.0 \times 10^9/l$ to $13.8 \times 10^9/l$, averaging up to $(11.6 \pm 0.37) \times 10^9/l$. At the same time,

signs of lymphocytosis were revealed in 11 (19.6 %) of these patients in the range from 38 % to 56 %, on average up to 46.3 ± 1.7 %, increased ESR was found in 10 (17.9 %) patients from 17 mm/h to 50 mm/h with a mean value of 27.8 ± 3.4 mm/h. In the biochemical parameters of the liver functional state, 9 (16.1 %) patients presented with a short-term slight increase in alanine aminotransferase activity from 0.7 mmol/h to 1.99 mmol/h, on average to 1.06 ± 0.15 mmol/h with negative test results for markers of viral hepatitis.

In all patients with prolonged and chronic Lyme disease, the diagnosis was confirmed by serological detection of IgG to *Borrelia burgdorferi* and in every second patient with IgM in a comprehensive diagnostic examination on average on day 82.4 of the disease in the prolonged course and on day 142.5 in the chronic course. These patients had no history of erythema during this disease, and only one patient mentioned the tick bite approximately 4 months ago. Clinical symptoms in the prolonged and chronic course of Lyme disease were not expressed and characterized by polymorphism of clinical manifestations. All patients with this course had astheno-vegetative manifestations and varying intensity of arthralgia, some patients periodically reported subfebrile temperature (4 out of 6), decreased appetite (3 out of 6), headache (4 out of 6), discomfort in the heart (2 out of 6), decreased visual acuity (2 out of 6).

In patients with prolonged and chronic Lyme disease, changes in the total blood count were seen in every second patient with ESR acceleration (3 out of 6) from 37 mm/h to 58 mm/h with a mean value of 42.8 ± 2.4 mm/h, with no pathological changes in blood count. However, in the biochemical parameters of the liver functional state, most of these patients (4 of 6) had an increased alanine aminotransferase activity to 1.34 ± 0.18 mmol/h.l, that in every second patient with chronic course (2 out of 4) was combined with an increase in total bilirubin from 30.5 $\mu\text{mol/l}$ to 61.0 $\mu\text{mol/l}$ with negative test results for markers of viral hepatitis.

Discussion

It is known that the diagnosis of Lyme disease is based on clinical and epidemiological data and serological diagnosis. Lyme disease is characterized by spring–autumn seasonality, which is associated with the activity of the vector, the peak number of cases occurs in the summer months [17,20]. According to the results of our analysis, a clear seasonality of Lyme disease in the Zaporizhzhia region was also established, with a predominance of patients in summer (56.5 %) and spring (25.8 %). It is considered important to diagnose Lyme disease at an early stage of the process, as untimely or lack of antibiotic therapy leads not only to dissemination of the process, but also to serious complications and negative prognosis for recovery and quality of life [4,21,22]. Despite the growing awareness of clinicians about Lyme disease over the past decade, errors in clinical and specific diagnosis are quite common in practical medicine [21].

Early diagnosis of Lyme disease is based on clinical and epidemiological data. However, the immature nymphal stage as well as the adult stage of the vector, is a small ectoparasite that can easily go unnoticed when attached to

humans, which in combination with nonspecific symptoms of Lyme disease and the absence of migratory erythema can lead to delays in diagnosis or misdiagnosis [23]. According to the analysis of Lyme disease cases in the Zaporizhzhia region, it was found that only 80.6 % of patients clearly indicated the tick bite, almost one in five patients could not remember the tick bite. At the same time, in the conditions of prolonged or chronic course in patients, there was no history of erythema, clinical symptoms were polymorphic with a predominance of astheno-vegetative manifestations, varying intensity of arthralgia, low-grade fever, headache and other. If clinical and epidemiological data were sufficient to confirm the erythematous form of Lyme disease, all other clinical variants of this infection required mandatory laboratory confirmation.

The specific laboratory diagnosis of Lyme disease remains difficult. To date, the inexpediency of using bacteriological examination due to low sensitivity and slow growth of the pathogen has been proven [1,15,24,25]. Diagnosis of Lyme disease remains challenging even with the help of molecular genetic methods, because the sensitivity depends on the type and volume of biological material sample, the presence of polymerase chain reaction inhibitors due to contamination [26]. The sensitivity of the polymerase chain reaction in the diagnosis of Lyme disease varies from 34 % to 64 % [27,28].

Due to the low sensitivity, technical complexity and time constraints of direct methods, most European and US countries use a two-level protocol for serological diagnosis of Lyme disease [2]. In the first stage, ELISA detect antibodies to pathogen antigens [9]. In case of doubtful result of ELISA in the second stage, a highly specific immunological method (immunoblotting) is used to check the presence of antibodies to specific *Borrelia* proteins [24,28]. The disadvantage of this protocol is the relatively low sensitivity of 25 % to 50 % in the early stages of the disease, because the synthesis of sufficient antibodies to identify them in the blood takes at least three weeks. In addition, in the early period of the disease, false-negative results are often found due to cross-reactions in the presence of autoimmune, rheumatic, hematological and some other infectious diseases [1,29]. In the later stages, when antibody titers increase due to the activity of B-lymphocytes, the sensitivity of this examination increases to 99 % [28,30].

According to the results analyzing our serological examinations, patients with prolonged and chronic Lyme disease had positive IgG to *Borrelia burgdorferi* (100 %) and IgM in 50.0 % of cases. However, in patients with acute Lyme disease, serological confirmation of the diagnosis was obtained in 75.0 % of simultaneous detection of both IgM and IgG to *Borrelia burgdorferi* (39.3 %) and positive IgM in the absence of IgG (35.7 %). Obtained seronegative results in 25.0 % of patients with acute Lyme disease required clear clinical and epidemiological data to confirm the diagnosis.

Conclusions

1. Lyme disease in the Zaporizhzhia region has a clear seasonality with a predominance of patients in summer (56.5 %) and spring (25.8 %). The vast majority of patients (80.6 %) clearly indicated the tick bite when visiting various

natural sites. The disease was mostly acute (90.3 %) with a predominance of erythema (94.6 %), in some cases there was the prolonged (3.2 %) and chronic (6.5 %) course.

2. The serological profile of patients with acute Lyme disease was characterized by seropositivity of 75.0 % with simultaneous detection of both IgM and IgG to *Borrelia burgdorferi* (39.3 %) and positive IgM in the absence of IgG (35.7 %). Seronegative 25.0 % of patients required clear clinical and epidemiological data to confirm the diagnosis. Patients with prolonged and chronic Lyme disease had positive IgG to *Borrelia burgdorferi* (100 %) and IgM in 50.0 % of cases.

3. Acute Lyme disease was characterized by a predominance of erythema (94.6 %) with the most common localization on the skin of the lower (54.7 %) and upper extremities (17.0 %), mild or no manifestations of general intoxication syndrome, lack of pathological changes in the hemogram in most patients (80.4 %), and if there were any, it was leukopenia (12.5 %) or leukocytosis (7.1 %) with the presence of lymphocytosis (19.6 %) and accelerated ESR (17.9 %).

4. In the case of prolonged and chronic Lyme disease, there was no history of erythema, clinical symptoms were polymorphic and included astheno-vegetative manifestations, varying intensity of arthralgia, low-grade fever, loss of appetite, headache, discomfort in the heart, decreased visual acuity. Half of the patients had the accelerated ESR in the absence of changes in blood count, mild cytolytic syndrome and moderate hyperbilirubinemia.

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