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Lyme borreliosis in children – trends in epidemiology. A single-centre study

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ABSTRACT

Introduction: The aim of the study was to assess the changing incidence of Lyme borreliosis (LB) in a children's group in Wielkopolska, and the influences of gender and age as well as erythema migrans (EM) occurrence on the development of various forms of LB in children.

Material and methods: Retrospective analysis covered the medical records of 206 children diagnosed with LB, hospitalised in the Department of Infectious Diseases and Child Neurology in Poznań and consulted at its Clinic of Infectious Diseases from 1 January 2012 to 30 October 2021. For an epidemiological analysis, the study population was limited to patients from Wielkopolska. A total of 196 qualified subjects were divided into 2 time periods, the first covering the years 2012–2016, in which LB was confirmed in 52 children, and the second covering 2017–2021, in which the disease was diagnosed in 144 children. The relationship between the course of LB and the gender and age of the patients was analysed in both groups. Statistical analysis of the data was performed, and the results were compared with published data.

Results: The epidemiological analysis showed a more than a twofold increase in the number of LB cases in the analysed time periods, mainly diagnosed as EM. The high incidence of LB neurological complications in children, including those with incorrectly diagnosed EM, remains constant. There was no relationship between the clinical forms of the disease and the child's sex, but an increase in the number of EM diagnoses in younger children was confirmed.

Conclusions: The study confirmed the increase in the number of LB diagnoses, analogous to the entire population of the region. The significant increase in the number of early stages of the disease and the frequent occurrence of neurological complications in children with undiagnosed and untreated EM indicate the need for ongoing education in the diagnosis of LB.

KEY WORDS:

Lyme borreliosis, erythema migrans, neuroborreliosis, child.

INTRODUCTION

For many years, an increasing incidence of tick-borne diseases has been observed in Europe [1]. One of the most common diseases is Lyme borreliosis (LB), caused by the spirochete *Borrelia burgdorferi sensu lato* (BB) transmitted to humans during bites of BB-infected ticks. The name of the disease refers to the city of Lyme in the United States of America, where an epidemic form of arthritis was reported in 1972 [2]. A few years later (1977), Steere *et al.* first characterised Lyme arthritis (LA) as a separate tick-borne disease [3].

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The main vector of infection with spirochetes of the *Borrelia* (B.) species in Europe, including Poland, are hard ticks of the species *Ixodes ricinus*. They do not show host specificity and can parasitise numerous species of vertebrates (reptiles, mammals, and birds). *Ixodes ricinus* ticks are three-host arachnids, which means that a tick sucks the blood of a different host during each developmental stage. Humans can be a host at any stage of tick development [4].

In Europe, the 3 main BB genotypes identified in *Ixodes icinus* ticks are *B. afzelii*, *B. garinii*, and *B. burgdorferi sensu stricto*. They prefer specific tissues in humans: *B. afzelii* is mainly dermatotropic, whereas *B. garinii* is neurotropic and *B. burgdorferi sensu stricto* arthrogenic. In the US, only *B. burgdorferi sensu stricto* was genotype-identified. However, all organ manifestations can develop in LB-infected patients with any of the different BB genotypes [5].

The infection occurs when a BB-infected tick penetrates the skin using a suction tube. The spirochetes, after entering the skin with tick saliva, initially spread to the site of entry, leading to a local skin infection, which is clinically manifested by the appearance of an erythematous lesion (erythema migrans – EM). Untreated infection leads to a disseminated phase of the disease and may take the form of erythema chronicum migrans, neuroborreliosis (NB), cranial nerve paralysis, LA, myocarditis, or arrhythmias (Lyme carditis – LC). The disease may be accompanied by general symptoms such as fever, headache, muscle aches, enlarged lymph nodes, fatigue, and neuralgia [6]. Symptoms of neuropathy in the orofacial area, such as numbness, prickling or tingling, sharp, stabbing, throbbing, or burning pain, can mimic toothache and may prompt patients to visit their dentist for answers to their ailments [7].

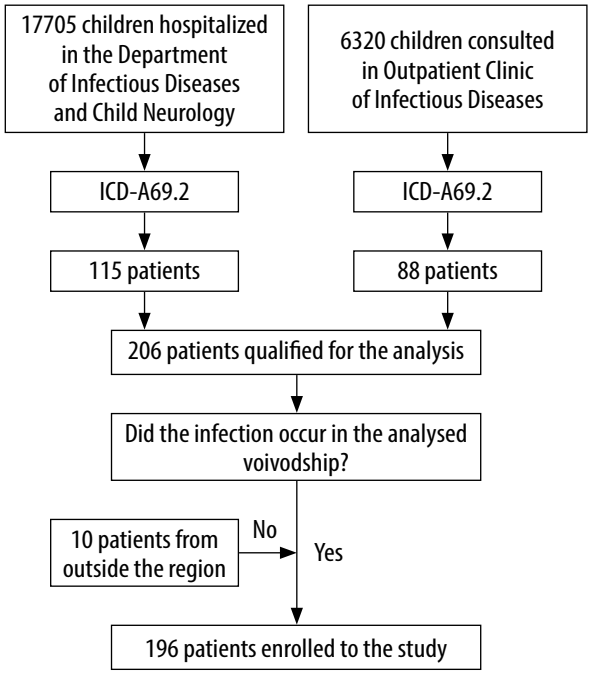

FIGURE 1. Study qualification rules: Lyme borreliosis in children – trends in epidemiology

A single-centre study. Time period analysed: 1 January 2021 – 30 October 2021

The occurrence of LB in the paediatric population is more frequent than that in adults, which is most likely related to the age-specific behaviour of children [8]. This age predisposition is emphasised more frequently in American literature, where LB is called "little boys' disease" [9]. Studies describing the situation in paediatric populations in European countries are rare, which may be related to the simultaneous occurrence of several BB genotypes and geographical differences.

In this study, we assessed the changing incidence of LB in a children's group and the influences of gender and age as well as EM occurrence on the development of various forms of LB in children.

MATERIAL AND METHODS

The retrospective analysis covered the medical records of 206 children diagnosed with LB (ICD-A69.2), hospitalized at the Department of Infectious Diseases and Paediatric Neurology Karol Jonscher Hospital University of Medical Sciences in Poznań (total number of hospitalizations during the given period: 17,705 children) or consulted at the Outpatient Clinic of Infectious Diseases Karol Jonscher Hospital in Poznań (consulting doctors: specialists in paediatrics and infectious diseases, total number of consultations during the given period: 6320 patients) from 1 January 2012, to 30 October 2021. In patients referred to the Outpatient Clinic, the initial diagnosis of LB was made by GP doctors, regional paediatricians, and cardiologists. The infectious disease specialist verified the diagnosis based on the patient's medical documentation and a medical examination. Lyme borreliosis was the first diagnosis in the patient's diagnosis list. Detailed rules for the enrolment of patients for the study are presented in Figure 1.

To meet the needs of an epidemiological analysis, the study population was limited to patients from the Greater Poland voivodeship. The basis for qualification to affiliation was the child's place of residence, declared by the guardians, and the area where the tick bite occurred, based on the zip code. Children from outside the district and people living in Greater Poland who reported having been bitten by ticks outside the voivodeship (n = 10) were not subjected to further analysis. On this basis, 196 children were qualified for further research.

Polish Society of Epidemiologists and Doctors of Infectious Diseases criteria were adopted as the basis for the diagnosis of LB [10]. We defined a case of LB with either a physician-diagnosed EM lesion or a positive two-tier serology in a child with symptoms compatible with LB.

In children with EM, the diagnosis was based on the presence of a typical ring-shaped erythema on

the child's skin, exceeding 5 cm in diameter, surrounding the tick bite (Figure 2).

In the case of other forms of the disease, namely LA, NB, LC, and acute facial nerve palsy (FNP), the diagnosis was based on the occurrence of clinical symptoms, confirmed by paediatric and specialist examination (neurological, cardiological, rheumatological), typical for pathology laboratory diagnostics, and a positive result of the two-stage LB serological diagnosis. In the first stage, the enzyme-linked immunosorbent assay (ELISA) test was performed, and after obtaining a positive result, the second stage of the diagnostic, the Western blot test, was performed. The inclusion criterium was a positive ELISA test, confirmed by the Western blot test. Blood sampling for LB tests was performed when the disease was suspected. Serological tests of the blood and cerebrospinal fluid (CSF) were performed in the Central Laboratory in H. Święcicki Clinical Hospital in Poznań.

Biochemical tests of blood and CSF were performed at the Central Laboratory of Karol Jonscher Hospital in Poznań using an XN-1000 Sysmex analyser.

Qualification for the LA group was based on the occurrence of symptoms of inflammation (swelling, redness, pain, restriction of mobility) of at least one joint in the patient and the exclusion of the autoimmune process.

The diagnosis of NB and FNP was made based on neurological symptoms characteristic of the pathology (headache, disturbance of consciousness, paralysis of cranial nerves). In all patients with central nervous system (CNS) pathology, computer tomography of the head was performed, and CSF was obtained in the lumbar puncture analysis. The basis for NB qualification was confirmation of inflammatory changes in the patient's CSF, including pleocytosis, defined as the level of leukocytes above 5 cells in 1 ml of CSF, positive results of ELISA and Western blot tests for LB, as well as intrathecal immunoglobulin synthesis.

The facial nerve palsy was defined as an acute palsy involving the facial muscles in both upper and lower parts of the face, either unilateral or bilateral. In patients with FNP, there was no pleocytosis and no intrathecal immunoglobulin synthesis in CSF.

The Lyme carditis was defined as the occurrence of clinical symptoms suggestive of cardiac pathology: light-headedness, fainting, shortness of breath, heart palpitations, or chest pain associated with electrocardiogram abnormalities and/or biochemical markers of myocardial injury.

STATISTICAL ANALYSIS

Several types of variables were used to analyse the results of the research, including gender – a qualitative nominal variable, age – a measurable variable described on an ordinal scale, and clinical form – a categorical variable. Nominal, ordinal, and categorical variables are described using the count (n) and frequency (%), whereas measurable variables are described with the use of basic parameters: arithmetic mean, standard deviation, median, as well as the minimum and maximum values. Pearson's χ^2 test was used to test the relationships among categorical variables. The significance test of the difference between the 2 structure indices was used to compare the proportions of responses in the 2 groups. Non-parametric tests, i.e. the Mann-Whitney U test (to check the significance of the difference in 2 groups) and the Kruskal-Wallis test (to check the significance of the difference in at least 3 groups) were used to check the significance of the difference in the age level of patients due to the lack of normality of the distribution.

FIGURE 2. Erythema migrans in a 7-year-old child

At all levels of the research and analysis, $p < 0.05$ was considered statistically significant. Statistical calculations were performed using the STATISTICA 10 PL statistical package.

RESULTS

In the study group of 196 children with LB, the mean age was 9.1 ±4.4 years (girls: 9.7 ±4.6 years, boys: 8.6 ±4.2 years). The structure of the number and sex of the studied patients is presented in Table 1.

For the epidemiological analysis, the group of 196 subjects was divided into 2 time periods, the first covering the years 2012–2016, in which LB was confirmed in 52 children, and the second covering 2017–2021, in which the disease was diagnosed in 144 children. In these 2 analysed periods, a significant increase in the number of LB cases was confirmed, whereas no statistical differences were found in the distribution of the patients' gender and age (Table 2). The mean age of children was higher in the period 2012–2016 (9.7 ±4.2 years) than in the period 2017–2021 (8.9 ±4.5 years), although this difference was not statistically significant ($p > 0.05$).

In separate periods, the frequency of LB clinical forms was analysed. The significant difference between the pe-

TABLE 1. Age and gender statistics of sample population from Greater Poland Voivodeship – retrospective analysis

Gender	*n*	Average age	Standard deviation	Median	Minimum age	Maximum age
Female	96	9.7	4.6	10.0	1	17
Male	100	8.6	4.2	8.0	2	17
Total	196	9.1	4.4	9.0	1	17

TABLE 2. Gender analysis of sample population in the periods 2012–2016 and 2017–2021 and the Pearson χ^2 test results ($N = 196$)

Gender	2012–2016 ($N = 52$)		2017–2021 ($N = 144$)		χ^2	df
	n	%	*n*	%		
Female	31	59.6	65	45.1	3.20	1
Male	21	40.4	79	54.9		

n – population size, χ2 – Pearson chi-square test value, df – degrees of freedom, p – statistical significance value

riods 2012–2016 and 2017–2021 in the incidence of the 2 clinical forms was confirmed. Whilst EM was more common in 2017–2021 (in 71.5% of children), LA was more common in 2012–2016 (in 17.3% of children) (Table 3).

CLINICAL ANALYSIS

At the time of diagnosis, the analysedz patients ($N = 196$) presented one to three clinical forms of LB. Among all children, EM was the most common, found in 124 (63.3%) children. The second most frequent occurrence was represented by neurological disorders: FNP in 32 (16.3%) patients and NB in 18 (9.2%). In some children, both clinical forms occurred simultaneously. The other forms were reported less frequently: LA in 17 (8.7%) children and LC in 3 (1.5%) children. Also, 24 (12.2%) patients showed symptoms uncharacteristic of LB: headache, feeling distressed, feverish state, and chronic fatigue (Table 4). Some patients presented more than one LB form, e.g. among children with EM, 9 had FNP at the same time, 4 – NB, and 1 – LC.

GENDER AND CLINICAL FORM OF LYME BORRELIOSIS

The test of the significance of the difference between the 2 structure indices showed a significant difference between girls and boys only in the frequency of non-specific symptoms ($p = 0.0207$), which were more common in girls (17.7%) than in boys (7.0%). There was no effect of gender on the clinical course of LB (Table 4).

AGE AND CLINICAL FORM OF LYME BORRELIOSIS

The mean age of the examined children was highest among patients with cardiac arrhythmias and amounted to 14.2 ±1.0 years. The lowest mean age was recorded among patients with EM, which was 8.3 ±4.3 years. Using the Kruskal-Wallis statistical test, the correlation of the age with various clinical forms was investigated, confirming the influence of age on the occurrence of individual clinical forms of LB. Patients with cardiac arrhythmias were excluded from the analysis due to the insufficient size of this subgroup ($n = 3$) (Table 5).

We analysed the relationship between the fact that the caregivers noticed the tick bite and the occurrence of EM and the diagnosis of the child's LB form. A tick bite was confirmed only in children who had developed EM. In cases of disseminated LB, neither parents nor patients reported a bite. The early phase of Lyme disease, EM, was most common in the neurological forms of LB, whereas patients did not report LA and LC (Table 6).

DISCUSSION

Lyme borreliosis has been a significant epidemiological problem in Poland and in the world for several years. The first cases of the disease in Poland were recorded in the mid 1980s. From 1996, a statutory obligation was introduced to report all LB cases to Sanitary and Epidemiological Inspection. According to the "Regulation of the Minister of Health of 10 December 2019 on reporting suspicions and diagnoses of infections, infectious diseases, and deaths due to them", suspected or diagnosed LB or death due to it requires a doctor to report to the State County Sanitary Inspector competent for depending on the place of residence of the person who was infected or diagnosed with the infection [11].

According to the data of the National Institute of Public Health – National Institute of Hygiene, the number of cases of LB has more than doubled in recent years in Poland and in Greater Poland. In 2012, 8794 cases were registered in the country (incidence 22.8/100,000) and 215 in the voivodship, and in 2013, 12,763 cases were

TABLE 3. Age analysis of sample population in the periods 2012–2016 and 2017–2021 and Mann-Whitney U test result ($N = 196$)

Time period	*n*	Average age	Standard deviation	Median	Minimum age	Maximum age	Z	*p*-value
2012–2016	52	9.7	4.2	10.0	1	17	1.22	0.2243
2017–2021	144	8.9	4.5	8.0	2	17		

Z – Mann-Whitney U test's value, p – probability level

registered in Poland (incidence 33.12/100,000) and 241 in the voivodship. A sharp increase in the incidence of LB was observed in 2016, when 21,200 cases were reported in the country (incidence 55.0/100,000) and 579 in the voivodship; since then, the incidence has remained at a similar level (2019: country, 20,632 cases, incidence 52.5/100,000; voivodeship: 640) [12, 13]. Despite the COVID-19 pandemic, a constant high incidence of LB was observed within the voivodship (Figure 3). The high incidence of LB in Greater Poland requires further observation. This voivodship has a smaller percentage of forest area in relation to the eastern part of Poland, which may point towards the increasing risk of infection in urban areas.

However, relatively little is known about the incidence in the child population, and reports do not consider the age distribution. Our analysis confirmed an analogous to the population-related, more than 2.5-fold increase in the number of diagnoses of LB in children. The disease occurs in children of all ages, although the mean age indicates that most children are diagnosed in the early school period. This is consistent with the observations of other authors who indicate the incidence of frequent illness among children 5–9 years old [8]. Male susceptibility to falling ill has not been confirmed.

TABLE 4. Statistical analysis of sample population subdivided by Lyme disease's clinical forms (multiple responses) in the periods 2012–2016 and 2017–2021 and the results of the significance test of the difference between 2 structure indicators

Clinical form	2012–2016 (*N* = 52)		2017–2021 (*N* = 144)	
	n	%	*n*	%
EM	21	40.4	103	71.5
LA	9	17.3	8	5.6
FNP	10	19.2	22	15.3
NB	5	9.6	13	9.0
LC	1	1.9	2	1.4
OTHERS	10	19.2	14	9.7

EM – erythema migrans, FNP – isolated facial nerve palsy, LA – Lyme arthritis, LC – Lyme carditis, n – population size, NB – neuroborreliosis, p – statistical significance value (p < 0.05)

Based on our results, EM is the most common clinical form of LB among children. It mainly concerns younger children, and the problem has grown significantly in recent years. A similar observation about the frequency of EM was presented by Slovenian authors in 2003, also emphasising the importance of age [14]. Currently, there are no more recent data on the distribution of clinical

TABLE 5. Statistical analysis of sample population subdivided by Lyme disease's clinical forms (multiple responses) and the results of the significance test of the difference between 2 structure indicators

Clinical form	Total (*N* = 196)		Female (*n* = 96)		Male (*n* = 100)		*p*-value	Interview analysis *n* = 196
	n	%	*n*	%	*n*	%		Confirmed tick bite (%)
EM	124	63.3	60	62.5	64	64.0	0.8276	95 (76.6)
LA	17	8.7	6	6.3	11	11.0	0.2340	1 (5.9)
FNP	32	16.3	15	15.6	17	17.0	0.7945	9 (28.1)
NB	18	9.2	6	6.3	12	12.0	0.1594	4 (22.2)
LC	3	1.5	2	2.1	1	1.0	0.5335	0 (0.0)
Others	24	12.2	17	17.7	7	7.0	0.0207	12 (50.0)

EM – erythema migrans, FNP – isolated facial nerve palsy, LA – Lyme arthritis, LC – Lyme carditis, n – population size, NB – neuroborreliosis, p – statistical significance value (p < 0.05)

TABLE 6. Age analysis of sample population subdivided by Lyme disease's clinical forms and the Kruskal-Wallis test results

Clinical form	Total (*N* = 196)		Female (*n* = 96)		Male (*n* = 100)
	Average age	Standard deviation	Average age	Standard deviation	Average age
EM	8.3	4.3	8.8	4.4	7.8
LA	12.3	3.8	14.2	1.7	11.3
FNP	10.2	4.4	10.0	4.9	10.3
NB	9.3	3.8	7.5	2.6	10.2
LC	14.2	1.0	14.0	1.4	14.5
Others	9.5	5.1	10.6	5.2	6.7
H	14.6		8.6		12.2
p	0.0056		0.0728		0.0160

EM – erythema migrans, FNP – isolated facial nerve palsy, H – Kruskal-Wallis test value, LC – Lyme carditis, n – population size, NB – neuroborreliosis, p – statistical significance value (p < 0.05)

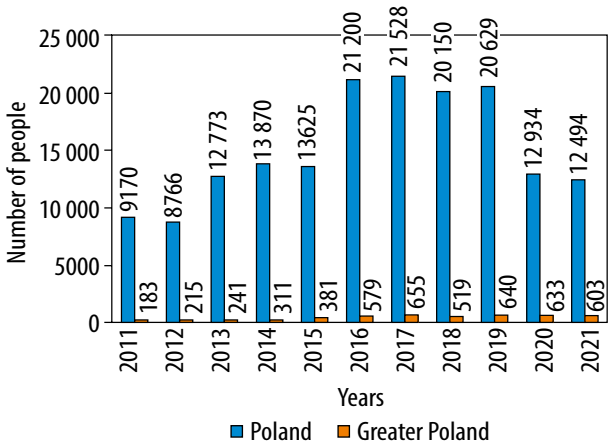

FIGURE 3. Lyme borreliosis cases in Poland and Greater Poland in 2011–2021

Based on the data of the National Institute of Public Health, Department of Epidemiology and Surveillance of Infectious Diseases (2021 – preliminary data).

forms in various European countries. The available data come from the countries of North America and emphasise the more frequent occurrence of disseminated forms, especially LA. However, it should be remembered that there are differences in *Borrelia sp*. serotypes between continents, which may affect the varied clinical picture of the disease [15]. The high percentage of patients with CNS pathology, FNP and NB, is disturbing. This problem has been highlighted by German and Norwegian authors working in BB endemic areas, who report that LB is the most common cause of non-pyogenic meningitis in children [16]. Such outstanding importance of BB ethology has not been demonstrated in the studies conducted in our centre [17]. There was also no evidence of a different course of the disease in girls, as emphasised by the Norwegian authors [18].

The conducted analysis also assessed the relationship between the occurrence of a specific form of LB and noticing a tick bite by parents or patients. It was shown that this association only occurred in people who later developed EM, and patients with disseminated forms did not remember the tick bite. No data analysing the above relationship were found in the available literature. Such a high percentage of patients with EM leads to the suspicion that people who notice the bite observe their children more closely, and the very diagnosis of a skin lesion is a consequence of this observation. This relationship may also be influenced by the demonstrated occurrence of EM in younger children and the fact that EM does not require serological confirmation. This poses a risk of overdiagnosis of LB in the early phase and implementation of treatment under pressure from parents. In the case of disseminated forms, the diagnosis of LB is sometimes made "retrospectively" (first neurological symptoms, then serological tests), often with a greater time interval from the bite.

Our analysis showed a high incidence of LB neurological complications, especially in people with untreated EM. There is a disturbing phenomenon, which has also been demonstrated by Swedish researchers, where the occurrence of EM before the episode of NB concerned 36% of the examined children [18]. This percentage is lower in the USA and amounts to only 15%, although the studies concerned the entire infected population, without distinguishing children [19]. Variations in the clinical manifestations of LB between the US and Europe are associated with differences in BB species causing the infection; this observation highlights the need for ongoing education in the diagnosis of EM in the paediatric population.

CONCLUSIONS

In this single-centre population-based study of children with LB, we found that the number of diagnosed cases more than doubled. This trend correlates with the constantly increasing incidence of LB within the voivodeship. This increase was primarily related to the number of EM diagnoses; EM occurs in younger children, and in 76.6% of cases, it is preceded by documented tick bites. The second most common form of LB comprise neurological disorders, namely FNP and NB, which are found in people without a documented bite, but in about 1/4 of the respondents, they were preceded by EM. Other clinical forms are already available. In the studied population, no relationship between sex and clinical form was found. However, the relationship between the occurrence of individual characters and the age of the child was confirmed. The observed differences between age and LB occurrence may be of importance for understanding the pathophysiology in LB.

DISCLOSURE

The authors declare no conflict of interest.

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