

Original article

Lyme neuroborreliosis in adults - epidemiology data and clinical findings

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Summary

Introduction. Lyme neuroborreliosis (LNB) can manifest during the early and late stages of Lyme disease (LD). The aim of this study is to determine epidemiology and clinical findings in patients with LNB.

Methods. The research was conducted in Banja Luka at the University Clinical Center of Republic of Srpska (UCC RS) during a four-year period from 10/2017 to 10/2021. The research included 51 patients admitted to the hospital with some neurological symptoms that could lead to the LNB diagnosis. Patients had lumbar puncture with cytochemical analysis of cerebrospinal fluid (CSF), ELISA anti-Borrelia IgM/IgG in serum and CSF, Immunoblot anti-Borrelia IgM/IgG in serum, and other documentation about epidemiology and clinical findings in LNB.

Results. A statistically significant ($p=0.017$) higher proportion of female patients was observed. Most patients were between 50 and 60 years old. Most of them were retirees (31.37%), farmers, medical technicians followed with forestry workers, students etc. Most of examinees did not have information on previous tick bite (64.71%). The largest number (72.55%) did not have data on previous skin changes. The largest number of neurological symptoms at admission related to the feeling of tingling and weakness in the extremities, headache, dizziness and some ophthalmological symptoms. Patients also suffered from consciousness and speech disorder, anxiety, paresis n.VII. The largest number of examinees had some neurological symptoms up to three months prior the admission to the hospital.

Conclusion. Symptoms of LNB can be quite non-specific or possibly even mimic other neurological diseases. Involvement of peripheral nervous system is dominant in adult patients. It is necessary to work on early diagnosis of LD and it is mandatory to report it to the national epidemiological service.

Keywords: lyme neuroborreliosis, epidemiology, clinical findings

Introduction

Lyme neuroborreliosis (LNB) can manifest during the early and late stages of Lyme disease (LD). LNB occurs in 10%–15% of all cases of Lyme disease (LD) and can affect any part of the nervous system [1, 2, 3, 4]. Symptoms differ in European and American population probably

because of different *Borrelia* genotypes [5, 6]. *Borrelia burgdorferi* primarily causes arthritis, *Borrelia afzelii* skin infections while *Borrelia garinii* is neurotropic [7, 8].

The goal of this study is to determine the epidemiological as well as clinical findings in patients with LNB.

Methods

This research was conducted as a prospective diagnostic study in Banja Luka at the University Clinical Center of Republic of Srpska (UCC RS) during a four-year period from 10/2017 to 10/2021.

The examinees were patients hospitalized in the UCC RS due to possible LNB.

Criteria for examinee inclusion:

- the presence of symptoms that could correspond to LNB
- performed lumbar puncture with cytochemical analysis of cerebrospinal fluid (CSF)
- ELISA anti-*Borrelia* IgM/IgG in serum and CSF, confirmatory Immunoblot anti-*Borrelia* IgM/IgG in serum
- other medical documentation: anamnestic data (sex, age, occupation, data on previous tick bites, erythema migrans manifestations, neurological and other symptoms reported by the patient during admission to the hospital, comorbidities, duration of symptoms before admission to the hospital, previous antibiotic therapy for LD and antibiotic efficacy during hospitalization).

Exclusion criteria:

- using antibiotics to treat LD prior to lumbar puncture
- absence of a favorable response to applied antibiotic therapy during hospitalization
- diagnosis of another disease.

Initially, 141 patients hospitalized in UCC RS due to neuroinfections were analyzed. Out of those 141 patients, 51 met the inclusion criteria.

The remaining 90 patients were excluded from the study because the CSF was not analyzed due to a contraindication for lumbar puncture, the patient used antibiotic therapy for LD before lumbar puncture, there was no favorable clinical response to the applied antibiotic therapy for LNB, or the diagnosis of another neurological disease was established.

The following were analyzed in this study:

- basic anamnestic data (sex, age, occupation, data on previous tick bites and the presence of erythema migrans, neurological and other symptoms reported by the patient during admission to the hospital, comorbidities, duration of symptoms before admission to the hospital, previous antibiotic therapy for LD, antibiotic efficacy during hospitalization) and the frequency of neurological symptoms at admission.

The data are presented with standard descriptive statistical measures. The analysis and comparison of the investigated groups were done in accordance with the type of data. The appropriate chi-square test was used to compare frequencies. The correlation of the results was determined by the Spearman correlation coefficient. The connection of the results was established by the Dice similarity coefficient, on the basis of which the dendrogram was created. The statistical significance was established for $p < 0.05$. Statistical analysis and graphical presentations of data were done by using statistical software package SPSS 22 (IBM, 2013) [9].

Results

In this study, 34 of patients (66.67%) were females, while 17 (33.33%) were males, with statistically significant ($p = 0.017$) higher proportion of female patients.

The age of patients is shown in figure 1.

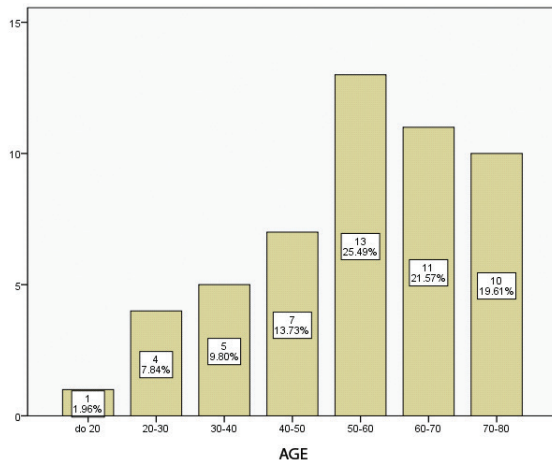


Figure 1. Patients by age

Manifestations of LNB in our patients occurred throughout the whole year.

Most of our patients were retirees (31.37%), farmers and medical technicians followed by forestry workers, students, traders, hairdressers and housewives (Figure 2).

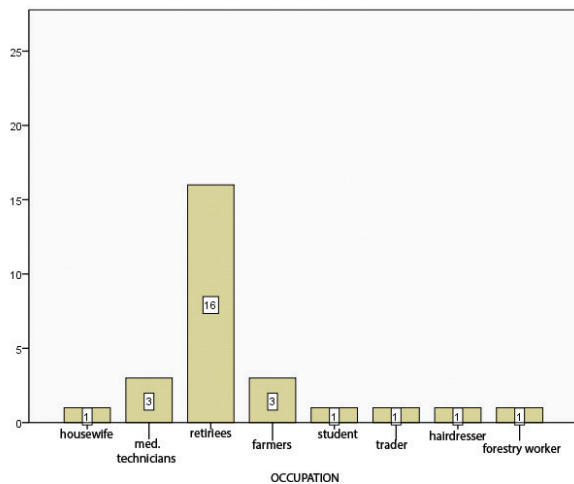


Figure 2. Occupation of patients

*1 housewife, 3 medical technicians, 16 retirees, 3 farmers, 1 student, 1 trader, 1 hairdresser, 1 forestry worker

Most of our patients did not have information on previous tick bite (64.71%).

The largest number of patients (72.55%) did not have any data on previous skin changes corresponding to the first stage of LD (erythema migrans). Only five subjects had data on erythema migrans.

Analyzing the frequency of neurological symptoms at admission, the largest number of symptoms related to the feeling of tingling and weakness in the extremities, headache, dizziness and some ophthalmological symptoms. In smaller numbers, patients also suffered from consciousness and speech disorder, anxiety, paresis n. VII and lower back pain. The largest number of examinees had some symptoms up to three months prior to admission to the hospital. By far the largest number of patients experienced symptoms for exactly one month (Figure 3).

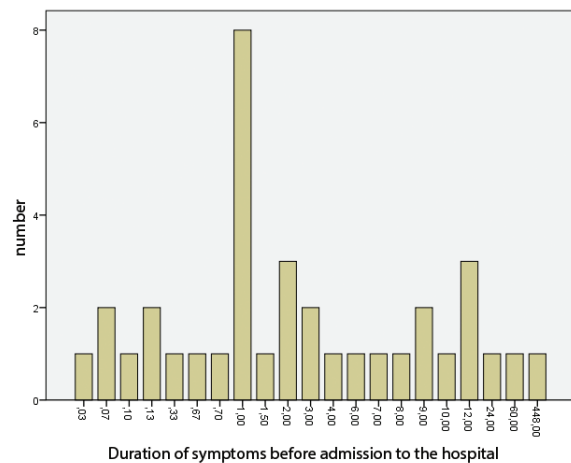


Figure 3. Duration of symptoms before admission to the hospital

The other symptoms were malaise (6 patients) followed by rash (5 patients), joint pain, cardiac problems and enlarged lymph nodes.

Discussion

Female patients (66.67%, $p=0.017$) were dominant in our study and that is in accordance with data from the literature stating that LNB is more common in middle-aged women than in men, although there are contrary data. Some papers state that, in those younger than 60, the incidence of LD is higher in men than in women, while the sex ratio in older age

groups is almost equal or only slightly higher in women [10, 11, 12].

In some European countries (Slovenia, Germany), the incidence of LD is higher among adult women (55%) [7]. Women are more aware of their health and seek health care more often and they are more exposed to infections. There are differences in sex susceptibility to infection and clinical manifestations of infection [11, 12, 13].

Our patients were adults aged from 19 to 78 years. Analyzing the age structure of our patients, it could be seen that most of them were between 50 and 60 years old. Patients over 40 make 80% of the sample. Younger patients were significantly less represented, only one in the category under 20. This data is in accordance with the literature [11, 14] and these may be a consequence of differences in leisure activities, i.e. differences in exposure to infection, as well as possible differences in sensitivity and germinal exposure to infection at different ages [12, 14].

In Northeastern America and most of Europe, the peak months of disease occurrence are June and July, which is a consequence of the feeding habits of nymphal ticks that usually feed in late spring or early summer. In some parts of Europe (Estonia, Sweden), the peak of the disease was recorded later, in August, possibly due to the northern latitudes of these countries. Smaller regional and annual variations are associated with meteorological conditions affecting tick feeding and people's stay in nature. Manifestations of LNB can occur early (several weeks or months after a tick bite) and late (several months or years after the tick bite) to the stage of disseminated infection several months or years after the tick bite, so the manifestations of LNB occur throughout the year [7]. Analyzing the seasonal frequency in our patients, manifestations of LNB occurred throughout the whole year because our patients were mostly in the third stage of late disseminated infection.

In our research, we found that most of our

patients were retirees (16 patients). Farmers and medical technicians followed in terms of occupational representation of patients. Other occupations recorded were forest workers, students, traders, hairdressers and housewives. People spending a lot of time outdoors and people living in rural or forest areas are more susceptible and have a greater risk of being exposed to ticks.

The exact time of infection often remains unknown because only about one third of patients remembered the tick bite [3, 10, 15, 16, 32].

The largest number of our patients (72.55%) did not know that they had erythema migrans. This emphasizes the importance of taking a detailed history from the patient, but also the fact that LNB can be the first and/or the only clinical sign in patients with early LD [16, 17].

The main neurological deficit that our patients reported on admission to the hospital was a feeling of tingling and weakness in the extremities (35 of them, i.e. close to 70%), followed by headache (17), three with paresis n. VII, 10 patients with ophthalmological symptoms (diplopia, ptosis of the eyelid, loss of vision in one eye, eye tremors, nystagmus, panuveitis, ophthalmoparesis), dizziness (7), disorder of consciousness (4), speech disorder (4), sacral pain with severe urination (3), anxiety (2). Only those patients who underwent lumbar puncture were included in the research.

Clinical manifestations of LNB are most commonly radiculitis (back pain alone or in combination with pain radiating to the extremities without or with additional paralysis of the extremities), cranial nerve paralysis (most often n. VII), headache, weakness [2, 10, 18]. It is also reported that dizziness and gait ataxia can be symptoms of LD in some cases [17].

Symptoms of LNB can be quite non-specific or even mimic other neurological diseases [10]. As shown in our work and data from the literature indicate that manifestations are very heterogeneous, and that LNB can be manifested by a wide range of different

symptoms from the central and peripheral nervous systems [19, 20].

In our patients, manifestations of the peripheral nervous system dominated, which, according to the literature, included cranial neuropathies, radiculoneuritis and other forms of involvement of peripheral nerves [15]. Elderly people often have nonspecific clinical signs that often overlap with chronic diseases [21, 22]. Two thirds of our patients were over 50 years old.

Neurological symptoms of LNB can appear early or late (duration of symptoms longer than six months) in the course of the disease [10, 23]. Looking at the duration of symptoms before admission to the hospital, we noticed that the largest number of our patients had symptoms lasting up to three months. Dominantly the largest number among them complained of symptoms exactly one month before admission to the hospital.

Clinical signs of early LNB include lymphocytic meningitis, radiculoneuritis, paresis n.VII and occasional severe headaches [23]. These manifestations can occur isolated or in combination and are considered common signs that should lead to the diagnosis of LNB even in skin lesions absence or no data on tick bites [15–18, 24–26, 33].

If cranial nerves are affected, it is most often n. VII. There are also isolated reports describing cases of vestibulocochlear nerve involvement with hearing loss or vertigo [17]. In England, for example, 22 cases of LNB including patients with paralysis of n.VII, with radiculoneuritis and meningoencephalitis, and two patients with peripheral sensory manifestations, and isolated nerve paralysis (n.VII, n.VI) were also reported [18]. Eighteen of our patients (35.3%) had meningitis, paresis n. VII was present in three patients, and headache was reported by 17 patients.

Radiculoneuritis is usually manifested by segmental pain, which has a poor response to all common analgesics. In 1–4 weeks about 75% of patients develop neurological defi-

cits mostly in the form of flaccid paralysis or segmental sensory disturbance. Radiculitis is often sacral with urinary symptoms, including urinary retention. Lumbar spine magnetic resonance is performed for ruling out other possible reasons for the mentioned complaints [33]. Three of our patients had low back pain with urination problems.

In our patients, as well as in the literature, radiculitis manifested itself as a feeling of pain and tingling in the extremities, back pain with occasional and difficult urination and pain radiating to the legs, arms and back in combination with unilateral weakness of the arms or legs, which can initially be mistaken for a stroke [10].

In addition to the ocular manifestations of LNB, there are usually additional symptoms [27]. Ocular manifestations associated with LNB are rare, but various have been described including conjunctivitis, keratitis and extraocular muscle paralysis as well as choroiditis, papillitis, blurred vision, strabismus [15, 26, 28]. Isolated papilledema is a rare manifestation, especially in adults, which usually manifests as diplopia [16, 27].

The differential diagnosis in patients with diplopia is quite broad. It includes an intracranial mass, idiopathic intracranial hypertension, infectious etiology, head trauma, or impaired CSF flow in the ventricles. Ophthalmological problems experienced by our patients were diplopia, eyelid ptosis, loss of vision in one eye, eye tremors, nystagmus, panuveitis, ophthalmoparesis [27].

Patients with ophthalmological symptoms as well as paresis of n. VII were not included in our study if they did not undergo a lumbar puncture. Dutch and other guidelines recommend serological testing for LD in situations where patients have bilateral paralysis n.VII or unilateral n.VII paralysis with other signs of possible LD, such as recent erythema migrans and/or tick bite [21, 29, 34]. It is stated in the literature that over 70% of patients with paralysis of n.VII due to LNB do not report a recent tick bite and/or erythema migrans [29].

Our patients with paralysis n.VII all provided information about a previous tick bite and the consequent appearance of erythema migrans. Of the three, two subjects had facial nerve palsy without other mentioned complaints, and one had facial nerve palsy as well as radiculopathy, which is also described in the literature as a possible combination of symptoms [10]. A Finnish prospective study, among 503 patients with paralysis of the n.VII, of which 11 had LNB, revealed a connection between headaches and LNB [29]. Information about headaches was given by 17 of our patients.

LNB is the presence of continuously active disease that lasts longer than six months with symptoms usually characterized by chronic meningitis, progressive encephalitis, myelitis or encephalomyelitis, and cerebral vasculitis [23]. The full clinical picture of progressive encephalomyelitis in LNB can mimic chronic progressive multiple sclerosis [30]. Myelitis and encephalitis are rare clinical manifestations of late LNB [10].

Transverse myelitis manifests with bilateral (often asymmetric) or unilateral limb weakness, sensory disturbances, and autonomic nervous system disturbance below the affected level of the spinal cord [16]. Acute cerebellitis is a rare manifestation of LNB with a very heterogeneous clinical course. Symptoms include headache, vomiting, fever, ataxia, dysarthria, tremor, meningismus, and impaired consciousness [19]. Cerebral vasculitis and stroke-like symptoms have been reported in young individuals without any underlying risk factors for stroke [28]. Headache, nausea, malaise, and vomiting, possibly signs of chronic meningitis, may be associated with secondary dementia and chronic LNB [30].

Chronic peripheral neuropathy is a possible late manifestation of LNB that is often associated with acrodermatitis chronica atrophicans - ACA [18, 31]. While some patients with peripheral neuropathy show evidence of meningeal involvement, CSF examination is often unremarkable when LNB is limited to

the peripheral nervous system. Therefore, it can be assumed that in peripheral Lyme neuropathy, the development of a *Borrelia*-specific immune response in the CSF is a time-dependent process [31]. Peripheral neuropathy is generally a common neurological disorder with multiple causes. In up to 25% patients, no etiology is identified [22]. Symptoms that our patients mentioned on admission were weakness, rash, pain in the joints, cardiac problems, and one case of enlarged lymph nodes. The listed symptoms are symptoms that are described as possible clinical manifestations of LD in one of its three stages.

The diagnosis of LD can be challenging and difficult. There is no universal standard; it is established on the basis of clinical symptoms and laboratory tests. The enzyme-linked immunosorbent assay (ELISA) is the first line, and then, in patients who have a positive or borderline ELISA test, a confirmatory Immunoblot test is performed. In the case of early LD, *Borrelia*-specific IgM antibodies can be detected from the third week, and IgG antibodies from the sixth week, and then the serological test is considered to be associated with more than 90% sensitivity and specificity. Regarding the Immunoblot test, a patient is considered to have a positive IgM blot in the first 30 days from the onset of symptoms. If symptoms are present for more than 30 days, an IgG blot should also be positive. If not, a positive IgM blot is likely a false positive [10, 11, 20].

Conclusion

Symptoms of LNB can be quite non-specific or even mimic other neurological diseases. Involvement of peripheral nervous system is clinically dominant over the involvement of central nervous system in adult patients with suspected LNB. It is necessary to work on early recognition of LD as well as on better and mandatory reporting to the national epidemiological service.

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Ethical approval. The Ethics Committee of the University Clinical Centre of Republic of Srpska, Bosnia and Herzegovina, approved the study (No: 01-19-191-2/19,

23.04.2019) and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

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Lajmska neuroborelioza kod odraslih - epidemiološki podaci i klinički nalazi

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Uvod. Lajmska neuroborelioza (LNB) se može manifestovati tokom ranog i kasnog stadijuma lajmske bolesti. Cilj ove studije je da se utvrde epidemiološki podaci i klinička slika kod pacijenata sa LNB.

Metode. Istraživanje je provedeno u Banjoj Luci, u Univerzitetskom kliničkom centru Republike Srpske (UCC RS) u periodu od oktobra 2017. do oktobra 2021. Istraživanje je obuhvatilo 51 pacijenta primljenog u bolnicu sa neurološkim simptomima koji bi mogli odgovarati kliničkoj slici LNB. Pacijenti su imali lumbalnu punkciju sa citohemijskom analizom cerebrospinalne tečnosti (CST), ELISA anti-Borrelia IgM/IgG u serumu i likvoru, imunoblot anti-Borrelia IgM/IgG u serumu, uz drugu dokumentaciju vezanu za epidemiološke podatke i kliničke manifestacije bolesti.

Rezultati. Uočen je statistički značajno ($p=0,017$) veći udio ženskih pacijenata. Većina pacijenata je bila između 50 i 60 godina. Većina njih su bili penzioneri (31,37%), poljoprivrednici, medicinski tehničari, potom šumarski radnici, studenti itd. Većina ispitanika nije imala informacije o prethodnom ugrizu krpelja (64,71%). Najveći broj (72,55%) nije imao podatke o prethodnim promjenama na koži. Vodeći neurološki simptomi pri prijemu bili su osjećaj trnaca i slabosti u ekstremitetima, glavobolja, vrtoglavica i neki oftalmološki simptomi. Pacijenti su takođe patili od poremećaja svijesti i govora, anksioznosti, pareze n. VII. Najveći broj ispitanika imao je neke neurološke simptome do tri mjeseca prije prijema u bolnicu.

Zaključak. Simptomi LNB mogu biti prilično nespecifični ili oponašati druge neurološke bolesti. Zahrvaćenost perifernog nervnog sistema je dominantna kod odraslih pacijenata. Potrebno je raditi na ranoj dijagnozi lajmske bolesti i obaveznom izvještavanju u nacionalnu epidemiološku službu.

Ključne riječi: lajmska neuroborelioza, epidemiologija, klinički nalazi