

LYME DISEASE - A TOPICAL HEALTH ISSUE IN ROMANIA

VICTORIA BÎRLUȚIU¹, R. M. BÎRLUȚIU²^{1,2}"Lucian Blaga" University of Sibiu**Keywords:** Lyme disease, *Borrelia*

Abstract: In the past three years, climatic changes have entailed important changes in the vector circulation, and, implicitly, in the incidence of arthropods. This is particularly valid in the case of Lyme disease, which is mainly transmitted in our geographical area via *Ixodes ricinus*, whose incidence has increased, in Romania, from 0.5‰ inhabitants in 2009 to 1.5‰ inhabitants in 2010, and to 2.2‰ inhabitants in 2011, respectively. The highest incidence, two deviations above the national mean incidence, has been found in Sibiu county. **Methods:** We undertook an observational study, from 2009 to 2011, of the confirmed cases of infection with *Borrelia* spp. We analyzed the batch from a demographic point of view and we investigated the clinical and stage aspects, diagnosis issues, the therapy and the evolution of every case. **Results:** If, in 2009, 15 cases of Lyme disease were clinically and serologically confirmed by ELISA and Western Blot tests, in 2010 their number increased to 71, and in 2011 to 128. More cases were confirmed in female patients (sex ratio 1:1.47), in the urban area (143 cases), in the summer months (June and July), in patients who were aware of the disease transmission moment (77.10% cases). The migratory erythema was present in 128 cases, associated or not with general manifestations. Stage II was diagnosed in 51 patients, who had articular, cerebral meningitis and cardiovascular manifestations. Stage III of neuroborreliosis was diagnosed in 37 patients. **Conclusions:** In the absence of constant investigations in the cardiology, neurology and ophthalmology units, Lyme disease remains under-assessed. The measures that address the vector must be complemented by specific prophylactic measures and serological investigations, at least in the case of persons exposed to occupational hazards—foresters, farmers and of those who recognize the tick bite.

Cuvinte cheie: boala Lyme, *Borrelia*

Rezumat: Modificările climatice din ultimii 3 ani, au antrenat importante modificări în circulația vectorilor și, implicit, în incidența antropozoonozelor. Este și cazul bolii Lyme, transmisă în zonă predominant prin *Ixodes ricinus*, a cărei incidență a crescut în România, de la 0.5‰ locuitori în 2009 la 1.5‰ locuitori în 2010, respectiv 2.2‰ locuitori în 2011. În centrul țării, se constată cea mai mare incidență, în județul Sibiu, de peste două deviații față de media națională. **Material și metodă:** Ne-am propus un studiu observațional, în perioada 2009-2011, al cazurilor confirmate cu infecție cu *Borrelia* spp, analizând lotul din punct de vedere demografic, aspecte clinice și de stadializare, probleme de diagnostic, terapia și evoluția cazurilor. **Rezultate:** Dacă în 2009, am confirmat clinic și serologic prin ELISA și Western Blot 15 cazuri de boală Lyme, în 2010, 71 cazuri, în 2011 numărul a crescut la 128. Au fost înregistrate mai multe cazuri la genul feminin (sex ratio 1:1.47), în mediul urban (143 cazuri), în lunile de vară (iunie și iulie), la pacienții care recunosc momentul transmiterii bolii în 77.10% din cazuri. Eritemul migrator a fost prezent la 128 cazuri, asociat sau nu cu manifestări generale. În stadiul al doilea, am diagnosticat 51 pacienți cu manifestări articulare, meningocerebrale, manifestări cardiovasculare. Al treilea stadiu, de neuroborrelioză tardivă, s-a diagnosticat la 37 pacienți. **Concluzii:** Boala Lyme rămâne subevaluată în absența unei investigații permanente în serviciile de cardiologie, neurologie, oftalmologie. Măsurile care se adresează vectorului, trebuie completate cu profilaxia specifică și investigarea serologică cel puțin a persoanelor expuse la risc profesional - silvicultori, fermieri, sau a celor care recunosc mușcătura de căpușă.

INTRODUCTION

Lyme disease is a zoonose, caused by at least 4 species of *Borrelia* type: *B.burgdorferi*, *B.afzelii*, *B.garinii* and *B.spielmanii*, transmitted to humans via the *Ixodidae* tick bite. This has 13 genera and approximately 650 de species, which can transmit various types of bacteria, rickettsia, protozoa and viruses:(1) *Borrelia*, *Anaplasma phagocytophilum* (*Ehrlichia phagocytophila*), *Babesia microti*, tick-borne

encephalitis virus (TBEV), *Rickettsia* spp. Crimean-Congo hemorrhagic fever (CCHF) virus (CCHFV). In Europe, *I. ricinus* is the most important vector of borreliosis; in North America, *I.pacificus*, *I.scapularis* are incriminated. In all evolutionary stages - larva, nymph and adult, *Ixodes* may transmit the infectious charge during a hematogenous lunch. The passage from diapause occurs after a single hematogenous lunch, with the passage from one stage of development to another, during an

¹Corresponding author: Victoria Bîrluțiu, Str. Lucian Blaga, Nr. 2A, Cod 550169, Sibiu, România, E-mail: victoriabirlutiu@yahoo.com, Tel: +40269 212320

Article received on 13.06.2012 and accepted for publication on 04.10.2012
ACTA MEDICA TRANSILVANICA December 2012;2(4):190-193

average minimal period of 8-12 months until a host is found. This can sometimes take years in the regions with temperate climate.(1,8,9) *B.burgdorferi* Gram negative extracellular spirochet was first identified in 1975, in Connecticut, in children with arthritis in the town of Old Lyme (12) and it was eventually inculcated by ticks in patients with Lyme disease as well.(2,11)

The incidence of the disease is increasing worldwide: in the U.S.A., most cases occur in the north-eastern states, where 27.444 cases were found in 2007, 28.921 in 2008, 29.959 in 2009; in 2010, 22.561 cases of Lyme disease and 7.597 possible cases were found, with an incidence of 7.3%0 000 population.(3) The disease has been confirmed in 50 other countries - in Europe- Germany, Holland, the U.K. (4,6,10,7), in the former Soviet Union, in China, Japan and Australia.

Lyme disease is a multisystemic disease, with stage evolution in the absence of incipient treatment with antibiotics. Stage I appears within 3-30 days from the tick bite, under the form of an erithematous placard that extends to the periphery, leaving the central tegument area normally colored, without prurit, known as migratory erithema. Secondary multiple, disseminated, tegumentary lesions are sometimes associated, without indicating the existence of other tick bites. At least 1 of 4 patients does not show migratory erithema. In some cases, the patients have fever, myalgia, arthralgia, headache or adenopathies around the bite. Months after the bite, stage II manifestations emerge: disseminated borreliosis with articular affecting (pain, tumefaction at the level of large articulations – knees, elbows, ankles, shoulders or other articulations), cardiac affecting (atrioventricular block, myocarditis, pericarditis, etc.), nervous system affecting (paralysis of cranial nerves, uni- or bi-lateral facial paralysis, meningitis). The late, chronic stage of the disease is characterized by neuropathies, myelo-polyradiculoneuritis, sleeplessness, memory loss, cardiac rhythm disorders, chronic arthritis, etc.

Laboratory tests identify specific antibodies by ELISA assay – these antibodies can remain positive many years after the disease was cured or after immuno-fluorescence. Laboratory tests also entail a Western blot assay confirmation test – IgM and IgG dosage for symptoms that have appeared in the past 30 days, and IgG for signs and symptoms that appeared prior to the 30-day time range.(3)

For the first two stages, Lyme disease is treated with Doxycycline (2x100mg/day/adults), 4mg/kg/day/children over 8 years(it is forbidden in pregnant women and children under 8years), Amoxicillin (3x500mg/day/adults, 50mg/kg/day/children), Cefuroxime-axetil (2x500mg/ day/adults, 30 mg/kg/day for children), for 14 days.(5) Doxycycline is preferable, as it is more active even in relation to HGA (human granulocytic anaplasmosis). In the second stage, with cardiac and articular affecting, third-generation cephalosporins are recommended: Ceftriaxone 2g/day/ for adults, 50-75 mg/kg/day/children (maximum 2g/day) or Cefotaxime 3x2g/day/adults, 150-200 mg/kg/day/children, Penicillin G, 14 days; if patients are allergic to β-lactamines, Doxycycline may be given, 200 mg/day 10-28 days. In stage III, third-generation cephalosporins are administered (Ceftriaxone or Cefotaxime) for 14-28 days, or high-dose Penicillin G.

Borrelia spp. is resistant to fluoroquinolones, glycopeptides, first-generation cephalosporins, rifampin, carbapenems, variably to macrolides. At the same time, dietary supplements, cholestiramine, immunoglobulines are inefficient.

PURPOSE

We undertook an observational study, from 2009 to 2011, of the confirmed cases of infection with *Borrelia* spp. We analyzed the batch from a demographic point of view and we

investigated clinical and stage aspects, diagnosis issues, the therapy and the evolution of every case.

METHODS

We undertook a study of the confirmed cases of Lyme disease in Sibiu county, the area with the highest incidence of the disease, from 2009 to 2011.

For stage I, of localized borreliosis, we selected those patients who showed a cutaneous lesion, which was initially maculo-papulous, of minimum 5 cm, tending towards peripheral extension, with or without partial paleness, which had emerged 2-30 days after the tick bite, and which could be subsumed to the notion of migratory erythema, associated or not with general manifestations: fever, cephalaea, arthralgia, myalgia. The patients diagnosed with disseminated borreliosis (stage II) had a several weeks to approximately 1 year history of tick bite, sometimes anamnestic migratory erythema, associated with general manifestations of pseudoinfluenza, cutaneous lesions similar to the initial lesion but of smaller sizes, muscular and skeletal manifestations: recurring, short-term arthralgia lasting for weeks or months, joint tumefactions that were sometimes accompanied by myalgia, fibromyalgia or neurological manifestations: paralysis of cranial nerves, lymphocytic meningitis, encephalo-myelitis, radiculo-neuropathy or cardiac manifestations, atrio-ventricular block, myopericarditis. Stage III of borreliosis was identified several years after the tick bite, in the patients with Lyme chronic arthritis, atrophic chronic acrodermatitis or chronic neurological syndroms – memory disturbances, depression, sensory polyneuropathy, spastic paraparesis etc.

We made the first serological tests 21 days after the tick bite in the patients with positive epidemiological criteria (tick bite) and clinical manifestations within the case definition, and we determined IgM and IgG by ELISA test. The diagnosis of Lyme disease was confirmed in the patients with IgM positive. In the cases where IgM was uncertain, a second serum sample was taken, and IgM Western blot (WB) was used for confirmation. For stage II, the diagnosis was validated based on positive/uncertain IgM and/or IgG using ELISA, associated with IgM (WB)+ and IgG (WB)-, for the onset of the manifestations before 8 weeks, without neurological manifestations; IgM (WB) +/- și IgG (WB) + 8 weeks after the onset without neurological manifestations; IgM (WB) + and IgG (WB) – from the serum, associated with IgM(WB) + and IgG (WB) – from LCR for stage II with neurological manifestations; for stage III with neurological manifestations, the case was confirmed based on IgM and/or IgG positive/uncertain associated with IgM (WB) – and IgG (WB) +, from the serum and LCR.

RESULTS

The cases of infection with *B.burgdorferi* spp, registered from 2009 to 2011 and the demographic analysis are presented in table no.1.

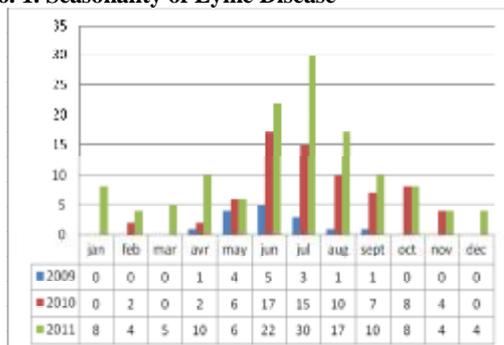
Table no. 1. Demographic data

Year	2009		2010		2011	
No. of cases	15		71		128	
Environment	U 10/15	R 5/15	U 49/71	R 22/71	U 87/128	R 41 /1 28
Sex ratio	M 6/15	F 9/15	M 30/71	F 41/71	M 50/128	F 78 /1 28
Mean age	40.73 (2-70 years old)		44.79 (3-85 years old)		47.57 (5-78 years old)	

During the three years, the cases of borreliosis were more frequent in the urban area, in female persons (sex ratio 1:1.5 in 2009; 1:1.36 in 2010; 1:1.56 in 2011), mean age over 40, with age extremes ranging from 2 to 85 years.

Relative to the case incidence, the most frequent cases occurred in the summer months (figure no. 1), June and July. The cases recorded in November and in the winter months were of patients diagnosed in stages II and III.

Figure no. 1. Seasonality of Lyme Disease



Of the 214 patients, 165 were aware of the tick bite moment (77.10%). The patients who came to hospital in stage I (126 cases) had migratory erythema and cephalaea – 107 patients, fever - 84 patients, myalgia – 79 patients, arthralgia – 55 patients, fatigue – 56 patients, pain or local tumefaction – 67 patients, satellite adenopathy – 28 patients, paresthesia – 23 patients, local/generalized pruritus – 24 patients.

Table no. 2. Clinical aspects in stage I

Clinical manifestations	2009	2010	2011
Migratory erythema	9/15 (60%)	31/71 (43.66%)	86/128 (67.19%)
Pain, local tumefaction	2/15 (16.66%)	23/71 (32.39%)	42/128 (32.81%)
Localized adenopathies	0/15 (0%)	16/71 (22.53%)	12/128 (9.38%)
Fatigue	3/15 (20%)	16/71 (22.53%)	37/128 (28.90%)
Cephalaea	7/15(46.66%)	35/71(49.29%)	65/128(50.78%)
Myalgia	6/15(40%)	28/71(39.44%)	45/128(35.15%)
Arthralgia	6/15(40%)	15/71(21.12%)	34/128(26.56%)
Paresthesia	1/15(6.66%)	11/71(15.49%)	11/128(8.59%)
Pruritus	1/15(6.66%)	10/71(14.08%)	13/128(10.15%)
Fever	4/15 (26.66%)	32/71 (45.07%)	48/128(37.5%)

We diagnosed 51 patients with stage II Lyme disease, most of whom (45) had articular manifestations. Large joints – knees, elbows, coxofemoral articulation - were affected most. The manifestation was persistent; it lasted for weeks/months, and had a migratory character (table no. 3). 4 patients presented walking difficulty, the impossibility of maintaining orthostatism; 2 of them also had meningocerebral affecting. 6 other patients showed cardiac affecting: myopericarditis (1), atrio-ventricular block (3), anamnestic rhythm. Two cases remained uninvestigated.

Table no. 3. Articular impairment in stage II

Articular affecting	45/45
Uni/bilateral knee	38/45
Uni/bilateral elbows	34/45
Uni/bilateral shoulders	27/45

Interphalanx articulations hands	21/45
Ankle	16/45
Fist articulation	14/45
Tempo-mandibular articulation	3/45

Stage III, neuroborreliosis, was diagnosed in 37 patients, 17 patients with demyelinating lesions confirmed by MRI, 1 case with cerebral ischemic lesion (ictus), optic neuritis (4 cases), sensory polyneuropathy (28 patients), spastic paraparesis - 7 patients, chronic arthritis in 12 cases (table no. 4).

Table no. 4. Symptoms in neuroborreliosis

Loss of concentration	32/37
Memory impairment	34/37
Visual impairment	4/37
Sleep disorders	14/37
Pareses	7/37
Headaches	24/37
Balance impairment	12/37
Paresthesia	28/37
Chronic arthritis	12/37

The clinical evolution was favorable for the stage I and II cases; stage I patients were treated with Aminopenicillin or Doxycycline for 14 days. For stage III, we prescribed Ceftriaxone 2g/day (34 cases) and Aminopenicillin/Doxycycline (17 cases). All patients with neuroborreliosis received treatment with third-generation cephalosporins (Ceftriaxone or Cefotaxime, 21 days), and improvement was visible after the therapy, less in the cases of spastic paresis.

DISCUSSIONS

Lyme disease is more often confirmed in urban areas, due to the proximity of the medical facilities and to a more informed population. It is more frequent in June and July, in the female persons. The emergence of Lyme disease allows for a better understanding of its mechanisms and an active control of the patients. Only 77.10% of our patients were aware of the tick bite. 2/3 of them had migratory erythema, the rest of the cases being difficult to diagnose in that stage. Out of the patients who were not aware of the tick bite instance or did not have migratory erythema, we diagnosed 15 patients with fever, cephalaea, myalgia, arthralgia. Biologically, they had hepatocytolysis, thrombocytopenia, with creatine phosphokinase increase in 4 cases. The cases diagnosed in stage II showed persistent affecting of large joints, with migratory character; meningeal and cardiac affecting was rare (2, 6 cases, respectively). In oligosymptomatic patients in Cardiology, Neurology or Ophthalmology units, the disease may be underdiagnosed. Given their polymorphism, stage III manifestations are by far most frequently attributed to psychiatric or neurological manifestations, being treated accordingly. With the increase of the incidence of the disease, the patients' recourse to medical units allows for a better assessment of the cases. In parallel, vector prevention measures remain the only solution for fewer cases in the absence of specific vaccination. The measures that address the vector must be complemented by research on the infectious charge of ticks

and on the serological investigation of the persons who are at increased professional risk – farmers, foresters – and of those who are aware of the tick bite, even in the absence of migratory erythema.

REFERENCES

1. Anderson JF, Magnarelli LA. Biology of ticks. *Infect Dis Clin North Am.* 2008;22(2):195-215.
2. Nava S, Guglielmone AA, Mangold AJ. An overview of systematics and evolution of ticks. *Front Biosci.* 2009;14:2857-2877.
3. Oorebeek M, Sharrad R, Kleindorfer S. What attracts larval *Ixodes hirsti* (Acari: Ixodidae) to their host? *Parasitol. Res.* 2009;104(3):623-628.
4. Steere AC, Malawista SE, Snyderman DR, et al. Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. *Arthritis Rheum.* 1977;20(1):7-17.
5. Burgdorfer W, Barbour AG, Hayes SF, Benach JL, Grunwaldt E, Davis JP. Lyme disease-a tick-borne spirochetosis? *Science.* 1982;216(4552):1317-1319.
6. Steere AC, Grodzicki RL, Kornblatt AN, et al. The spirochetal etiology of Lyme disease. *N Engl J Med.* 1983;308(13):733-740.
7. CDC- Reported Lyme disease cases by state, 2000-2010.
8. Wormser GP, et al. The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America- *Clinical Infectious Diseases*; vol 43. p. 1089-1134.
9. Fülöp & Poggensee *Parasitol Res.* 2008;103Suppl1:117-20.
10. Hofhuis, et al. 2006. *Euro Surveill.* 22:11 E060622.2 E060629.5;
11. Smith, et al. *Emerg Infect Dis.* 2000;6:404-7.
12. HPA/Lyme borreliosis website; 2008.