Diagnostic, therapeutic and evolutive particularities of Lyme disease

Particularități diagnostice, terapeutice şi evolutive ale bolii Lyme

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Abstract

Background: *Among the emergent diseases which mankind is confronted with, nowadays we can mention Lyme borreliosis (LB), a zoonosis produced by bacteria from Borrelia type, transmitted by Ixodes ticks.* ***Aim:*** *to analyse incidence, clinical forms, diagnostic and post-therapeutic evolution of the patients with early LB.* ***Material and methods:*** *260 patients, both gender, tick-bite, who we admitted in First Infectious Disease Clinic Targu Mures between May, 20 and September, 20, 2008, were retrospectively analysed. The diagnostic of LB was established using Centers for Disease Control and Prevention criteria: epidemiology, (history of tick bite), physical signs (skin, nervous and articular determinations) and for confirmation laboratory tests for determining antibodies anti Bb (IgM) from serum and cerebrospinal fluid (CSF), using enzyme-linked immunoassay (ELISA) technique, Virion/Serion kit.* ***Results****: Tick-bite was recognised by all 260 pts; there was a dominance of females (56.9%) against males (43.1%), with more patients from urban areas (57.7%) compared with rural areas (42.3%), 53.85% pts had skin manifestations, neurological signs were observed in 4.6% of the patients and articular involvement was encountered in 3.07% of all subjects. Serology was positive (IgM antibodies anti Bb) in 90 pts (34.6%). The therapy consisted of: Doxicyclin, Ceftriaxone, Amoxicilline+ Clavulanic acid, Azytromicyn.* ***Conclusions****: in our area, the incidence of Lyme borreliosis was higher in 2008 vs. 2007. Predominant clinical aspects were: cutaneous, and after them nervous and articular manifestations. Presence of IgM anti Bb antibodies confirmed the certain disease. Etiological therapy was efficient in all patients; no complications or sequele were noticed. Early etiologic therapy in Lyme borreliosis plays an important role in spirochetal eradication, in prevention of chronic infection.*

Keywords: *Lyme borreliosis, diagnosis, treatment*

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Rezumat

Printre bolile emergente cu care se confruntă omenirea momentan se situează şi borrelioza Lyme (BL), zoonoză produsă de bacterii din genul Borrelia, transmisă de căpuşele Ixodes. ***Obiectivele*** *studiului au constat în monitorizarea: incidenței, a formelor clinice, diagnosticul şi evoluția postterapeutică a pacienților cu borrelioză Lyme precoce.* ***Material şi metodă****: studiul s-a efectuat în perioada 20 mai – 20 septembrie 2008 în Clinica Boli Infecțioase I Târgu Mureş pe un număr de 260 de pacienți de ambele sexe, muşcați de căpuşe. Diagnosticul de BL s-a stabilit respectând criteriile CDC: epidemiologice (istoric de muşcătură de căpuşă), clinice (determinări cutanate, neurologice şi articulare) şi serologice pentru determinarea anticorpilor antiBb (IgM) atât din ser cât şi din lichidul cefalo-rahidian (LCR) prin tehnica ELISA, kit Virion\Serion.* ***Rezultate****: Muşcătura de căpuşă a fost recunoscută de toți cei 260 pacienți, a predominat sexul feminin (56,9%), față de sexul masculin (43,1%), cu o pondere mai ridicată a persoanelor din mediul urban (57,7%) comparativ cu cele din mediul rural (42,3%). Manifestări clinice cutanate au prezentat 53,85% din pacienți, neurologice 4,6% din bolnavi, articulare – 3,07% din subiecți. Serologia a fost pozitivă (anticorpi anti Bb tip IgM) la 90 pacienți (34,6%). Terapia a constat din Doxiciclină, Ceftriaxon, Amoxicilină + Acid clavulanic, Azitromicină.* ***Concluzii****: în arealul nostru s-a remarcat o incidență mai ridicată a bolii în anul 2008 vs 2007. Manifestările clinice predominante au fost cele cutanate, urmate de cele neurologice şi articulare. Prezența anticorpilor anti Bb IgM a permis precizarea cu certitudine a afecțiunii. Terapia curativă administrată a fost eficientă la pacienții monitorizați, nu s-au înregistrat complicații sau sechele. Instituirea precoce a terapiei etiologice în borrelioza Lyme deține un rol important în eradicarea spirochetei, prevenind cronicizarea infecției.*

Cuvinte cheie: *borrelioza Lyme, diagnostic, tratament*

Introduction

Among the emerging infectious diseases mankind has to fight against, there is Lyme disease or borreliosis, caused by bacteria from the genus Borrelia genus, transmitted by ticks from the genus Ixodes. Lyme borreliosis (LB) is the most frequent infection transmitted by ticks from the genus Ixodes, in the USA; there were 60.000 cases between 2003 and 2005 and it is mandatory to report each case. Lyme borreliosis frequency is lower in Europe compared to the USA, probably due to the fact that reporting is not mandatory. According to the Regional Offices of the WHO in Europe (2007), there has been an increase in LB related morbidity in the last decade, in every endemic area. According to the CDC (Centers for Disease Control and Prevention), Romania is in the disease transmitting zone, some of its endemic areas are already known (Mures, Cluj, Sibiu, Harghita, Maramures, Arad) (5). In a paper published in 2001, Hristea et al (10) pointed the presence of a areas with highest density of Ixodes ricius (study was performed in 1999). Stage 1 consists of local manifestations at skin level in the form of the erythema chronicum migrans (ECM), with or without constitutional symptoms. A second stage follows by blood dissemination, affecting the central and peripheral nervous system (producing meningeal, encephalic, radicular, medullar lesions, and damage to the cranial nerves), cardiovascular system (myopericarditis, arrhythmias) and joints (arthritis). Stage 3 occurs due to lack of proper diagnosis and treatment, when the enumerated symptoms become chronic (1, 4). The last two decades were marked by sustained research concerning the pathogenesis, immunology, clinical spectrum, diagnosis, treatment and prophylaxis of this disease. Given the available data, borreliosis is a treatable disease, although there are differences regarding response and evolution after therapy, depending on stage and used antibiotic (2, 7, 11).

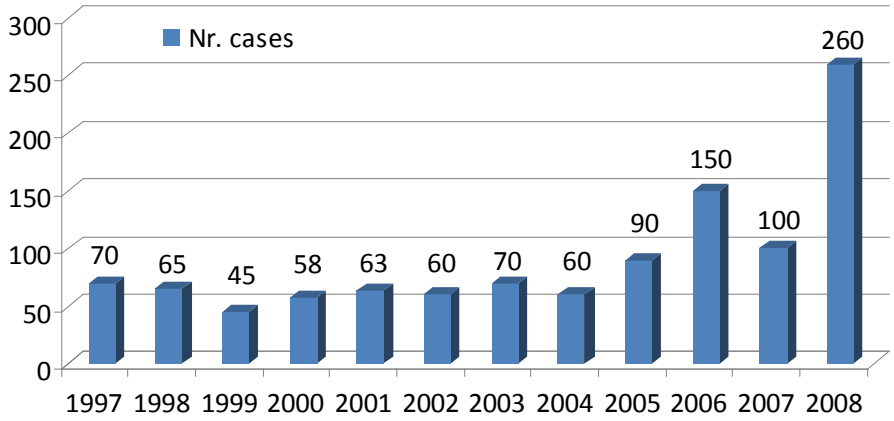

Figure 1. Incidence of Lyme borreliosis in Mureş district

Objectives

In the present study we aim to emphasize the incidence, clinical forms, diagnosis and evolution of patients with early Lyme borreliosis.

Material and methods

The study has been conducted between May 20th and September 20th 2008 in the Clinic of Infectious Diseases I of Targu Mures, on a number of 260 patients bitten by ticks.

The diagnosis of LB was established using the Centers for Disease Control and Prevention criteria: epidemiology, (history of tick bite), physical signs (skin, nervous and articular determinations) and for confirmation laboratory tests for determining antibodies anti *Borrelia burgdorferi* (Bb) IgM from serum and cerebrospinal fluid using enzyme-linked immunoassay (ELISA) technique, monitoring the increase of antibodies titer and seroconversion, using Virion/Serion reagents.

Results

The incidence of LB cases in Mures district was higher in 2008, compared with previous years (*Figure 1*). 260 patients were admitted, with or without ECM. 57.69% of patients came from an urban environment, and 42.31% from a rural environment.

The incidence of LB was higher among the female population (56.92%), than in the male population (43.08%).

Also, LB was more frequent among children and teenagers (48.08%), young adults

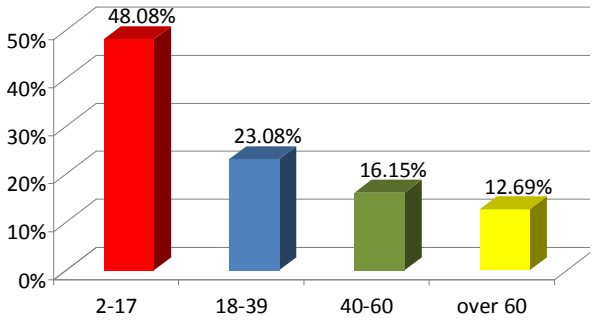

Figure 2. Distribution of Lyme borreliosis by age

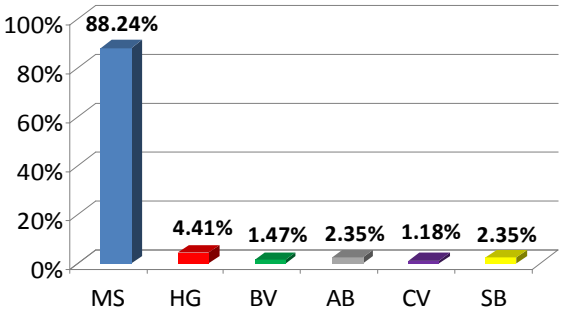

Figure 3. District of provenience of patients with Lyme borreliosis in the studied group

Table I. Treatment of erythema chronicum migrans (ECM)

ECM	Adults	Children	Period
Amoxycillin / clavulanic acid	5.55%	91.12%	14 days
Azithromycin	5.55%	4.44%	7 days
Cefuroximum	11.13%	4.44%	14 days
Doxycycline	77.77%		14 days

Table II. Treatment of Lyme neuroborreliosis (LNB)

LNB	Adults	Children	Duration
Acute lymphocytic meningitis		Ceftriaxone 1,53%	30 days
Cranial nerve paralysis (VII)	Doxycycline 0,38%	Ceftriaxone 1,15%	21 days
Radiculitis	Doxycycline 0,38%	Ceftriaxone 0,76%	21 days
Distal neuropathy	Doxycycline 0,76%		21 days

(23.08%) and adults (16.15%), compared with patients over 60 years (12.69%) (*Figure 2*).

From the total of 260 patients 88.24% came from Mures district and 11.76% from neighbouring areas, such as Harghita, Alba, Sibiu, Covasna, Brasov (*Figure 3*).

We observed the history or presence of ECM in 53.85% of patients, 46.15% were bitten by a tick, but did not develop skin manifestations. The most frequent localizations of ECM were: cephalic extremity, cervical region (40% of cases), torso (28.33%), upper limbs (19.17%) and lower limbs (12.50%) (*Figure 4*).

In the studied group neurological symptoms were present in 12 patients (4.62%), as follows: acute lymphocytic meningitis (in 4 patients), facial nerve paralysis (3), radiculitis (3) and distal neuropathy (2). Articular symptoms were present in 3.07% of patients and affected the knee, elbow and shoulder.

Serology assessed with ELISA technique was positive in 90 (34.62%) patients; among this, 65 patients (72.22%) had IgM anti-Bb antibodies levels between 5-10 U/l and 25 pts (27.78%) had levels between 10-20 U/l after a period of 30 days. Anti Bb IgG antibodies

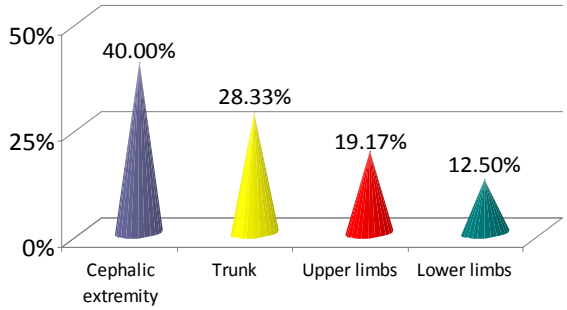

Figure 4. Localization of *erythema chronicum migrans*

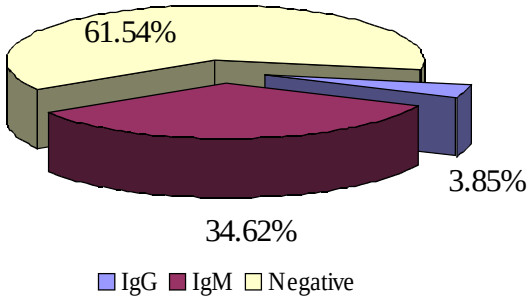

Figure 5. Serum IgM, IgG anti *Borelia burgdorferi* antibodies levels (ELISA method)

were observed in 10 patients (3.85%), who did not have clinical signs of disease, just a history of tick bite; 160 patients (61.54%) had a negative serology for Bb (*Figure 5*). We were able to follow-up the variation of IgM antibodies levels in only 27.78% of patients, these levels were rising after 60 days, reaching 40-50 U/l.

Treatment

Treatment of ECM in children was performed with Amoxicillin/clavulanate potassium in 91.12% of cases; patients who were allergic to Amoxicillin/clavulanate potassium were treated with Azithromicin (4.44%) or Cefuroxime (4.44%) for 10 days. In adults, ECM was treated with Doxycycline in 77.77% of cases, 5.55% were treated with Amoxicillin/ clavulanate potassium; Azithromycin was used in 5.55% of all adult patients. Cefuroxime was used in 11.13% of cases. Patients with neurological symptoms were treated 30 days with Ceftriaxone (in case of acute lymphocytic meningitis - 1,53%) and Doxycycline (in case of peripheral nervous lesions) for 21 days (*Tables I and II*). Patients with arthritis (3.07%) were treated with Doxycycline for 21 days.

Discussions

In Mures district and its neighbouring areas, where most of the patients (88.24%) came from, there is an increasing presence of vector agents (ticks from the genus Ixodes) and clinical manifestations, the incidence of LB being higher compared to past years (12).

Our study showed a high number of patients originating from an urban environment; this observation is in accordance with other studies which show that Lyme borreliosis is no longer an occupational disease and tends to affect more people from urban environment (5).

In our study, only three patients from a rural area had professions that included them in a high risk group. Epidemiological investigations demonstrate that the disease is more frequent among persons who spent some time in nature. The maximum incidence of the moment of infection occurred between May and August.

The most important marker for diagnosis was the presence of ECM in 90 patients. In the first 30 days after acquiring the infection most of the patients presented moderate neurological manifestations and symptoms like headache and infectious syndrome. Cranial nerve lesions (mostly those of cranial nerve VII – facial) and acute lymphocytic meningitis were present in children and adolescents, while painful radiculitis and neuropathy were present in adults, with a lower incidence, despite Halperin et al studies (8, 9). Cerebrospinal fluid presented minimal changes, with a pleiocytosis of 200-600 lymphocytes/mm^3 and normal biochemistry. IgM anti-Bb antibodies were present in the CSF and blood of a single patient.

Joint lesions (although more frequent among children in the USA), were more present in adults in our study, who presented local manifestations such as painful joints and muscles and functional impotence, occurring generally 24 days after acquiring the infection (11).

Serological investigations performed with ELISA technique showed type IgM anti-Bb antibodies in 90 patients (34.61%) in medium and high concentrations. In 27.78% of patients we could follow dynamically the rising of IgM antibody levels (13). Anti Bb IgG antibodies were positive just in 3.84% of the patients (maybe a previous exposure). As it is shown in some series, in Lyme disease antiBb IgM antibodies can persist months/ years (11, 12).

Etiological therapy consisted of Aminopenicillin and macrolids in children and cyclines in adults. Patients with neuroborreliosis were treated with 3rd generation cephalosporines, their evolution was favourable without any motor deficits or unrecoverable neurological sequelae (3, 6).

Conclusions

The incidence of Lyme borreliosis was higher in 2008, in our geographical region, compared to previous years.

Lyme borreliosis is an emerging disease that is becoming more than a professional disease, and tends to affect more and more children and young adults.

The presence of skin, neurological and joint manifestations as well as the positive serology confirm the presence of the disease and prove that in our geographic area approximately one third of ticks are infected.

Therapy was efficient in all patients included in this study; there were no complications.

Early administration of antibiotic therapy in Lyme borreliosis prevents the bacteria's dissemination and chronicisation.

Conflicts of interest

The authors have nothing to declare.

References

1. van Assen S, Bosma F, Staals LM, et al. Acute disseminated encepahalomieylitis associated with *Borrelia burgdorferi*. J Neurol 2004; 251(5):626-629;
2. Barsic B, Maretic T, Majerus L, Strugar J. Comparison of azithromycin and doxycycline in the treatment of erythema migrans. Infection 2000; 28(3):153-156;
3. Blanc F, Froelich S, Vuillemet F, Carre S, et al. Acute myelitis and Lyme disease. Rev Neurol 2007; 163(11):1039-1047;
4. Dernedde S, Piper C, Kuhl U, et al. The Lyme carditis as a rare differential diagnosis to an anterior myocardial infarction. Zeit Kardiol 2002; 1053-1060;
5. Dobracki W, Dobracka B, Paczosa W, Zieba J, Bereś P. Epidemiology of borreliosis in workers of the district forestry offices in Lower Silesia. Prezgl Epidemiol 2007; 61(2):385-389;
6. Fallon BA, Nields AJ, Burrascano JJ, Liegner K, DelBene D, Liebowitz MR. The neuropsychiatric manifestations of Lyme borreliosis. Psychiatr Q 1992;63(1):95-117;
7. Garlicki A. The modern therapy of lyme disease. Prezegl Epidemiol 2007; 61(3):449-456;
8. Halperin JJ, Logigian EL, Finkel MF, Pearl RA. Practice parameters for the diagnosis of patients with nervous system Lyme borreliosis. Neurology 1996; 46:619-627;
9. Halperin JJ. - Neuroborreliosis: central nervous system involvement. Semin Neurol 1997;17(1):19-24;
10. Hristea A, Hristescu S, Ciufecu C, Vasile A. Seroprevalence of Borrelia burgdoferi in Romania. Eur J Epidemiol 2001;17(9):891-896;
11. Steere AC. Lyme disease. N Engl J Med 2001;345(2):115-125;
12. Țilea B. – Borrelioza Lyme. University press, 2008; 20-26;
13. Wilske B, Schriefer M. Borrelia. In Murray PR, Baron EJ, Jorgensen JH, Pfaller MA. & Yolken RH, (eds), Manual of Clinical. Microbiology, 8th ed, ASM Press. Washington, vol 1, 2003; 937-954.