Lyme Neuroborreliosis – A Retrospective Study

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Background: Lyme Neuroborreliosis represents the acute or chronic infection of the central nervous system (CNS) and peripheric nervous system (PNS), as a consequence of a systemic infection.
Objectives: to evaluate the epidemiological, clinical, serological and post-therapeutic implications of CNS and PNS damage during Borrelia burgdorferi (Bb) infection.
Material and method: We performed a retrospective study on 23 patients admitted between January 1st, 2009 - December 31, 2010. The patient's inclusion was made respecting the criteria of the European Center for Diseases Control (ECDC) and the European Union Concerted Action on Lyme Borreliosis (EUCALB). The levels of antiBb antibodies (IgM, IgG) were measured in the cerebro-spinal fluid (CSF) and in the serum using ELISA and Western blot methods. Imaging techniques were used in the case of patients with meningeal and cerebral lesions. The patients were treated with 3rd generation cephalosporins and cyclins. Statistical analysis was performed using the Chi square and Student tests.
Results: Twenty patients (86.96%) were included in the acute phase and 3 patients (13.04%) in the chronic phase of the disease. Meningeal damage was observed in 16 patients (69.56%), cerebral damage in 4 patients (17.39%), cranial nerve lesions in 2 patients (8.69%), radiculoneuritis in 1 patient (4.34%). Serological investigations using the ELISA method revealed the presence of antiBb antibodies in 100% of cases, in the CSF antiBb IgM antibodies were found in 18 patients (78.26%), IgG in 3 patients (13.04%); using the Western-blot method IgM antibodies were found in 20 patients (86.96%) and IgG in 3 patients (13.04%).
Conclusions: Early diagnosis and therapy led to a favorable evolution compared with patients who were treated late, the latter presenting neurological sequelae and relapses.

Keywords: Lyme neuroborreliosis, diagnosis, treatment

Introduction

Lyme neuroborreliosis (LNB) is one of the emerging diseases mankind is struggling with at the moment, a disease with a natural focality, transmitted by arthropods of the Ixodes class, produced by bacteria from the Borrelia genus, characterized by multisystemic clinical manifestations with a stadial evolution and polymorph clinical picture. An important consequence of Borrelia burgdorferi (Bb) infection is the impairment of the central nervous system (CNS) and Lyme Neuroborreliosis (LNB), which can lead to chronicization and severe complications with considerable neurological sequelae in the absence of treatment. LB is the most frequent infection transmitted by Ixodes in the USA, with 16,000–20,000 cases reported each year in endemic areas, while in Europe (in the northern, central and eastern parts) the incidence of the disease is rising, with 85,000 reported cases each year (EUCALB, ECDC) [1]. The disease is also present in Romania in the form of sporadic cases, and in recent years several vector agents such as ticks from the genus Ixodes ricinus appeared in our geographic area, which led to a higher rate of monitoring and studying on our part. The real prevalence of neurological lesions in LB according to Steere and Malawista is approximately 15–25% [2,3]. Bb spirochaetes were demonstrated in the CNS in both acute and chronic phase of the disease, therefore it is important to separate the early LNB, a disease which starts within the first 12 months folowing the moment of infection, and late LNB which starts after 12 months following the moment of infection. Early LNB includes: acute lymphocytic meningitis, the most frequent manifestation of LNB, frequently associated with the inflammation of cranial nerves and radiculoneuritis in the form of Banwarth syndrome (meningoradiculitis), acute encephalomyelitis, cranial nerve lesions (III, IV, VI, VII, IX, XII). Late LNB includes chronic lymphocytic meningitis, progressive encephalomyelitis, Lyme encephalopathy [4].

The secure diagnosis of LNB is difficult, and it is made mostly on the basis of epidemiological (the presence of tick bite), clinical (erythema migrans – EM, meningoradiculitis, encephalitis, etc) and serological data, the presence of pleiocytosis in the CSF and the intrathecal synthesis of specific IgM and IgG antibodies, evidenced by ELISA and Western blot methods, which seem to possess higher sensibility and specificity than PCR (Polymerase chain reaction) [5].

Neuroimaging tests (CT, MRI) have an important role in the diagnosis of LNB, being able to evidence structural modifications in the periventricular, frontal or temporal areas of the substantia alba in 30–40% of cases [6]. The aim of antibacterial therapy in LNB is double: to cease the patient's complaints and to erradicate the spirochaetes to avoid chronicization. The most frequently used therapeutic agents in LNB are 3rd generation cephalosporins, betalactamins and cyclins, administered parenterally for 30 days, repeating as necessary in the case of recurrences [7].

Material and method

We performed a retrospective study on 23 patients admitted to the 1st Clinic of Infectious Diseases of Tîrgu Mureș. In order to avoid excessive diagnosis, the patients' inclusion in the study was made respecting the following criteria of the ECDC and EUCALB: epidemiological (the presence

Table I. Central Nervous System and Peripheric Nervous System impairment

Acute lymphocytic meningitis	69.56%
Acute encefalitis	17.39%
Facial nerve paralysis (VII)	8.69%
Radiculonevritis	4.36%

of tick bite), clinical (EM in the patient's history, presence of intracranial hypertension syndrome, meningeal, encephalitic and radicular lesions, cranial nerve paralysis) and serological (pleiocytosis in the CSF, its biochemistry, as well as demonstrating the presence of IgM and IgG antiBb antibodies using ELISA and Western blot methods). Patients with meningeal and encephalytic lesions were examined using computer tomography (CT) and magnetic resonance imaging (MRI).

In order to secure our diagnosis, we infirmed the false positive reactions that may occur in the context of other diseases, such as lues, multiple sclerosis, tuberculosis, mononucleosis, leptospirosis, autoimmune diseases. The studied group received etiological treatment with 3rd generation cephalosporins (Ceftriaxone), cyclins (Doxicycline) and their clinical and serological evolution was monitored. Statistical analysis was performed using the Chi square and Student tests.

Results

Twenty patients (86.96%) were included in the study in the acute phase of the disease (early NBL), presenting clinical symptoms within the first 12 months following the tick bite, while 3 patients (13.04%) were included in the chronic phase of the disease (late NBL), presenting neurological symptoms after 12 months following the tick bite. The age of the studied patients was between 9–60 years, with an average of 34 years. We observed a higher prevalence of urban origin (15 patients – 65.21%), compared with rural origin (8 patients – 34.79%), with a predominance of female patients (13 patients – 56.52%) over male patients (10 patients – 43.48%). The presence of tick bite in the patient's history and the presence of EM have been demonstrated in 19 patients (82.61%). The presence of tick bite in the patient's history and the absence of EM have been observed in 4 patients (17.39%). The maximum incidence of the moment of infection was in the warm season, between April and October. Acute meningitis was present in 16 patients (69.56%).

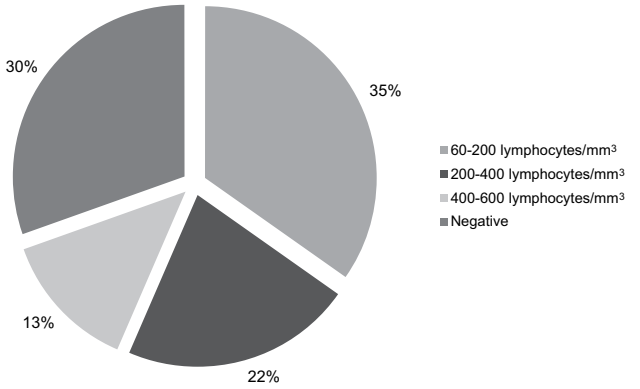

Fig. 1. Pleiocytosis in the cerebrospinal fluid (CSF)

Pleiocytosis of the CSF showed the following levels of the lymphocytes: low (60–200 lymphocytes/mm^3) in 8 patients (34.78%), medium (200–400 lymphocytes/mm^3) in 5 patients (21.73%); high (400–600 lymphocytes/mm^3) in 3 patients (13.04%).

Biochemistry from the CSF evidenced the presence of high protein levels in 10 patients (43.48%) with values between 100–200 mg% and normal glucose levels. Cerebral lesions were observed in 4 patients (17.39%), who developed moderate forms of acute encephalitis. Correlating the cerebral and meningeal lesions, we have observed the presence of associated lesions, in the form of acute meningoencephalitis in 4 patients (17.39%). Cranial nerve lesions were observed in 2 patients (8.69%), both presenting the unilateral lesion of the facial nerve (VII).

Benwarth's syndrome (meningoradiculoneuritis) was present in the case of 1 patient (4.34%).

Correlating the serological determinations from the CSF and serum using ELISA we confirmed the intrathecal production of IgM antiBb antibodies in 18 patients (78.26%), with an equivoque result in 2 patients (8.69%) and IgG antiBb antibodies in 3 patients (13.04%); using

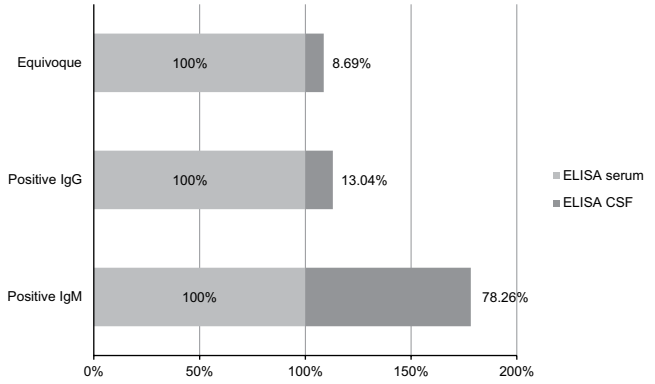

Fig. 2. Correlation between the anti-Bb antibodies (IgM, IgG) in the serum and CSF (ELISA)

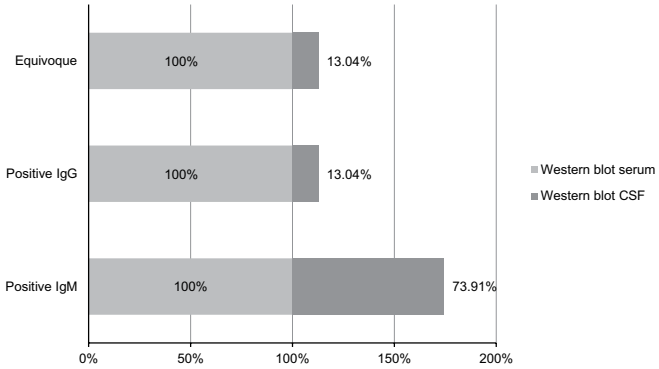

Fig. 3. Correlation between anti-Bb antibodies (IgM, IgG) in the serum and CSF (Western blot)

the Western blot method we found IgM antiBb antibodies in 17 patients (73.91%), with an equivoque result in 3 patients (13.04%) and IgG antiBb antibodies in 3 patients (13.04%).

We excluded the diagnosis of lues, tuberculosis, mononucleosis, multiple sclerosis and other autoimmune diseases, given the fact that serum determinations yielded negative results for these diseases. CT and MRI examinations showed the following: diffuse or localized cerebral edema in 3 patients (13.04%), hypodense lesions predominantly at the border of substantia alba and substantia nigra in 5 patients (21.73%), calcifications in 2 patients (8.69%), demyelination in 2 patients (8.69%). Patients with cerebral and meningeal lesions received etiological treatment with Ceftriaxone in 19 cases (82.61%), while patients with PNS lesions received Doxicycline in 4 cases (17.39%).

We observed a favorable evolution in 16 patients (69.56%) with the remission of the clinical and biological status of the CSF within 14 days of therapy, but slow evolutions as well with prolonged pleiocytosis of the CSF and prolonged acute inflammatory process at cerebral level, lasting over 14 days after initiating therapy. Three patients (13.04%) with late LNB presented relapses, i.e. recurrence of the inital symptoms after a variable period (with an average of 3 months) following the end of therapy.

Discussions

The impairment of the CNS and PNS during the infection with Bb has been demonstrated in 1922 by Garin and Bojadoux [cited by 2], who observed rachialgia, limb paralysis and CSF modifications following a tick bite. Our results confirm the presence of the disease and its sporadic manifestations in our geographic area [8,9]. In the studied group we observed a higher prevalence of the disease among young patients compared with patients over 50 years, which correlates well with data from the literature saying the disease is more frequent among children under 14 years and adults between 30–50 years [10].

We observed a higher prevalence of urban origin (15 patients – 65.21%), compared with rural origin (8 patients – 34.79%). This observation is backed by several recent studies pointing out the fact that Lyme borreliosis tends to affect more and more subjects from an urban environment, who go out to spend some time in nature. Acute lymphocytic meningitis showed a high incidence (69.56% of patients), in correlation with the data of Halperin et al. [4,8] stating that meningeal lesions are the most frequent manifestations of early LNB. The presence of antiBb antibodies in the CSF of 18 patients – 78.26% (confirmed with ELISA and Western blot) compared with IgG anti Bb antibodies in 3 patients (13.04%) allowed us to divide the patients in the 2 categories, early and late LNB, although Durnon, Miller et al. [2,3] observed the presence of IgM antibodies in the CSF even after years following the infection. Patients who presented negative CSF values but positive serum values (2 patients – 8.69%) were included in early LNB according to the criteria of the ECDC [1] due to the contact with the infecting agent and the clinical context, unilateral facial paresis (VII) in 2 teenage patients (8.69%), who had IgM antibodies in their serum, confirmed with both ELISA and Western blot methods [11].

CT and MRI examinations evidenced lesions in 10 patients (43.47%), with T2 high signal intensity in the cerebral white matter and T1 and T2 low signal intensity modifications in the subthalamic region, T2 high signal intensity modifications in the periventricular white matter and the border between white matter and grey matter, correlating with data from the literature [3].

Antimicrobial therapy with Ceftriaxone and Doxicycline for a period of 30 days was well tolerated, and needed repetition for patients with relapses (3 patients – 13.04%), according to the recommendations of Fallon and Shapiro [6,7].

Conclusions

The impairment of the central and peripheric nervous system during the infection with Borrelia burgdorferi was certain, with moderate clinical and neurological manifestations. Our study included mostly patients in the acute phase of Lyme neuroborreliosis. The evolution of patients under therapy was favorable, there were no motor deficits or irrecuperable neurological sequelae recorded.

Conflicts of interest

The authors have nothing to declare.

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