Diagnostic and treatment aspects of Lyme Neuroborreliosis

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Abstract

Lyme borreliosis is the most common tick-borne disease in Europe and North America. Nervous system involvement neuroborreliosis - is the most common manifestation of the disseminated Lyme disease. In Georgia, there is no information about the prevalence of borreliosis even though it is considered as an endemic disease and there is enough evidence to suspect that it is underdiagnosed. This article reviews certain challenging aspects of clinical manifestation, diagnosis and treatment of Lyme neuroborreliosis. (TCM-GMJ January 2016; 1:P25-P27)

Keywords: Lyme borreliosis, neuroborreliosis

Introduction

Lyme borreliosis is the most common tick-borne disease in Europe and North America. It is caused by spirochetes of the Borrelia burgdorferi sensu lato genospecies complex. Human disease is mainly caused by three of the genospecies: B. afzelii, B. garinii and B. burgdorferi sensu stricto. All three are prevalent in Europe while the disease is most commonly caused by B. afzelii and B. garinii. In North America, B. burgdorferi is the exclusive causative agent of borreliosis.1 Ixodes ricinus is the vector of Lyme disease in Europe and Ixodes scapularis – in North America. Lyme disease was first recognized in 1975 during an epidemic of arthritis in Lyme, Connecticut, USA.2

In Georgia, the prevalence of Lyme disease is unknown. Oral communication with clinicians reveals that they see Lyme disease in their practice. However, there is very little published information about it. Recent report lists borreliosis among endemic diseases in Abkhazia, a breakaway region of Georgia.3

It is well known that Lyme disease is common in countries neighboring to Georgia – Turkey,4,5 and Russia.6,7 The vector of Lyme disease, Ixodes ricinus, is detected at 67 locations all over Georgia.8 All these indicate that Lyme borreliosis is an important and potentially underdiagnosed disease in this country.

Further development of eco-tourism, associated with increased exposure to the disease vector, might lead to more cases of Lyme disease in Georgia.

Lyme borreliosis can affect many organs and systems, mainly leading to dermatological, neurological, cardiac, and musculoskeletal disease. The most frequent manifestation, indicating to local infection and accounting for approximately 90% of cases, is erythema migrans; while the central nervous system (CNS) is the most frequent manifestation of a disseminated disease.9 Nervous system involvement is referred to as Lyme Neuroborreliosis (LNB). LNB accounts for 10-15% of Lyme disease patients and affects both CNS and peripheral nervous system (PNS).10 In this review we are focusing on challenges of diagnosis and treatment of LNB.

The incidence of LNB in Europe is 3-11/100 000 per year.11 LNB is considered as a persistent infection. As Pachner described: “It has become clear that B. burgdorferi has joined Treponema pallidum, Herpes Simplex Virus, (HSV) and Human Immunodeficiency Virus (HIV) as an agent of persistent infection of the brain”.12

According to the time and location of manifestations, Lyme disease is classified into 3 stages. Stage I corresponds to the local infection, stage II – to the primary dissemination and stage III – secondary dissemination of the infection. The course of the disease may skip any individual stage, e.g., a patient with neuroborreliosis need not have had erythema migrans in the past.9

Clinical Features

Clinical features of LNB differ in European and American Patients. This is most probably due to the

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difference in bacteria species causing the disease in Europe and America - *B. burgdorferi* sensu stricto being the only causative agent in North America. It is not fully understood how *borrelia* disseminates from the site of the tick bite to other organs, including the nervous system. It has been suggested that *B. burgdorferi* disseminates predominantly via the blood, while *B. afzelii* and *B. garinii* migrate along other structures directly to the nerve roots. This explains the difference in clinical picture - in Europe, meningopolyradiculitis (Bannwarth’s syndrome) predominates, while in North America, CNS disease is more diffuse with mostly meningitis or encephalopathy. Because of these differences, North American clinical studies are not automatically applicable to the situation in Europe, including Georgia.

In Europe, Meningoradiculoneuritis (Bannwarth syndrome) is the leading manifestation of the early disseminated disease. After erythema migrans, this is the second most common manifestation of acute Lyme disease in adults. Its main clinical features are lymphomonoerytic meningitis, radiculitis, cranial nerve deficits (most commonly a peripheral facial palsy), radicular pain, and paresthesia. The protein concentration in the cerebrospinal fluid (CSF) is often relatively high, a finding that distinguishes this condition from a viral infection of the central nervous system.

In late disseminated stage (stage III of Lyme disease) of the disease, chronically progressive meningogencephalitis and multifocal cerebral vasculitis can arise. The term "chronically progressive meningogencephalitis" is used when irreversible neurological damage is present and the course of the illness is not self-limited, as it is in acute Borrelia-induced meningogencephalitis.

Another disease entity discussed in literature is Post Lyme Disease Syndrome (PLD). It is a condition persisting after treated Lyme Disease and is characterized by mostly mild and nonspecific symptoms, given that other causes have been excluded. PLD as a disease entity is not yet well defined and its pathophysiology is far from clear. Further studies on this topic are needed.

**Diagnostic evaluation**

The diagnostic criteria of LNB include three aspects: an appropriate clinical picture, a lymphocytic pleocytosis in CSF and an elevated specific Borrelia CSF-to-serum antibody index (AI), indicating intrathecal Borrelia antibody production (positive AI).

*Borrelia burgdorferi* sensu lato can be very difficult to culture from body fluids and requires specialized laboratories. As to the polymerase chain reaction (PCR), it is of limited sensitivity because of a low bacterial count in samples and accordingly has a relatively low diagnostic value. Thus, routine diagnostic testing of LNB is detection of *Borrelia*-specific antibodies.

In Europe, testing for Lyme disease must take the heterogeneity of the causative agents into consideration. It should be taken into account that there is a relatively high prevalence of antibodies against *Borrelia burgdorferi* (5% to 25%) even in healthy persons’ serum, depending on their prior exposure to tick bites in their occupational and leisure-time activities. ELISA that differentiates IgG and IgM antibodies should be used as a screening test. Positive or borderline results should then be confirmed with an immunoblot, the interpretation of which is described in the guidelines. Antibodies against Borrelia are found in fewer than 50% of patients with erythema migrans. In contrast, when neurological manifestations arise, Borrelia-specific IgM or IgG antibodies are found in the serum of more than 90% of patients. Serology together with the corresponding clinical manifestations has a high diagnostic specificity. In neuroborreliosis, the CSF examination reveals pleocytosis, usually with a leukocyte concentration well below 1000/µL, in which lymphocytes predominate. The CSF protein concentration is often elevated to 1 g/L or higher.

The clinical suspicion of neuroborreliosis is confirmed by the demonstration of CSF pleocytosis and intrathecally formed specific antibodies against *borrelia*. The borrelia-specific AI is determined for both IgG and IgM. It should be noted that an elevated Borrelia-specific AI does not mean an acute infection. Even when neuroborreliosis has been successfully treated, a positive Borrelia-specific AI can be found for years afterward.

There is a novel biomarker with a high diagnostic potential for LNB. It is the B-cell-attracting chemokine CXCL13, produced by monocytes and dendritic cells upon detection of intrathecal spirochetes and is a key factor for B-cell immigration into the CSF in LNB. The presence of this chemokine precedes the production of antibodies, and the sensitivity in early LNB is higher than the AI. However, highly elevated CXCL13 levels can also be found in the CSF in neurosyphilis, cryptococcal meningitis, cerebral lymphoma, tuberculous meningitis and HIV meningitis. Due to the low incidence of the aforementioned diseases, the positive and, in particular, the negative predictive value of CXCL13 for acute LNB still appears to be high. Thus, this test is promising but not yet included in the latest EFNS guidelines.

**Treatment**

Lyme disease generally has a good prognosis. Antibiotic treatment shortens the clinical course and prevents complications and rare chronic infections. On the other hand, reinfection is possible after another tick bite.
While the diagnosis of LNB might be challenging, the therapy is well defined. Several studies have documents a response to 14-day courses of intravenous ceftriaxone (2 or 4 g daily), intravenous penicillin (20 million units daily), intravenous cefotaxime (3×2 g or 2×3 g daily) or oral doxycycline (200 mg daily).  

Significant resistance of _B. burgdorferi_ to one of these antibiotics is reported to be very rare. It is recommended to treat for 14 days. There is no evidence that antibiotic treatment beyond 21-28 days is more effective, especially in the prevention of persisting syndrome.  

The outcome after antibiotic treatment is generally good. The pain, typical for Bannwarth’s syndrome, reveals under antibiotic therapy, and patients might be free of complaints even after one antibiotic dose. A delayed treatment initiation in particular is considered a risk factor for developing persistent symptoms.  

The prophylactic administration of antibiotics is not recommended as a routine measure. There is debate about whether this might be of benefit in certain exceptional cases, e.g. multiple tick bites in a highly endemic area for the disease, but the necessary duration of antibiotic is unclear.  

**Conclusion**  

The knowledge about LNB is still incomplete even though in recent years, many aspects of this disease have been elucidated. In particular, the discovery of CXCL13 as an early and activity marker for acute LNB has a high potential to improve diagnostic procedures. It is important to remember about the differences in pathogenesis and clinical picture of LNB in Europe and North America, while reviewing the international literature. In Georgia, baseline surveillance studies are needed to define the prevalence and describe the clinical characteristics of LNB in our country.

**References**