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Lyme neuroborreliosis: A diagnostic challenge

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Abstract

Lyme borreliosis (LB), also known as Lyme disease (LD) is the most prevalent tick-borne infectious disease in Bulgaria. In Europe, the most common causes of LB are the spirochetal bacteria of the Borrelia burgdorferi sensu lato genospecies complex (B. burgdorferi senso stricto, B. garinii and B. afzelii), which have different organotropism. B. garinii is especially neurotropic. Neuroborreliosis (LNB) is a disseminated form of LB and can present with neurological symptoms in both early and late disease with central and/or peripheral nervous systems involvement. Clinical manifestations of LNB are diverse and nonspecific, and may be mimic other neurological diseases, which often makes the diagnostic process challenging. In most patients, examination of the cerebrospinal fluid (CSF) establishes lymphocytic pleocytosis, damage to the blood-CSF barrier and an intrathecal synthesis immunoglobulines. The antibiotic treatment is efficient in the majority of cases.

Keywords: Lyme disease; Lyme neuroborreliosis; neurological symptoms; CSF pleocytosis

1. Introduction

Lyme borreliosis (LB), also known as Lyme disease (LD) is a tick-borne transmitted infectious disease, caused by spirochetal bacteria of the Borrelia burgdorferi sensu lato genospecies complex (Bbsl). The Bbsl includes the three most frequent agents of LB worldwide, B. burgdorferi (sensu stricto), B. afzelii, and B. garinii. In Europe, most LB cases are caused by B. afzelii or B. garinii. Nearly all LB cases acquired in North America are caused by B. burgdorferi. In Asia, B. garinii predominates as the causative species [1]. Each of the three most important pathogenic species is associated with certain differences in clinical expression. In Europe neuroborreliosis is more frequent than in the United States. The classic Lyme neuroborreliosis (Bannwarth's syndrome) in Europe is associated with B. garinii, whereas B. afzelii more typically causes skin manifestations [2]. The USA, almost all domestically acquired infections are caused by B. burgdorferi, accounting for the greater frequency of Lyme arthritis cases in North America compared to Europe or Asia [3].

LB is the most common vector-borne disease in Europe, North America and Asia. An average of nearly 132,000 cases reported to national surveillance systems annually and an estimated 30 % of persons in Europe reside in areas of high LB incidence (≥10 cases per 100,000 population per year) [4]. The Centers for Disease Control and Prevention (CDC) estimates about 300,000 new cases annually in the United States [5]. The reported incidence of LB in Bulgaria is about 6/100,000 of the population, but the true incidence is most probably much higher [6].

LB is transmitted by ticks of the genus Ixodes. In Europe, the principal vector of Borrelia is the hard tick I. ricinus [7]. LB is a common in the temperate climate zones. In Bulgaria, LB is an endemic disease and is reportable [8]. Regarding the prevalence of LB across different regions of Bulgaria, seroprevalence rates among all 28 provinces range from 0.0% to 20.0% [9]. Several regions showed significantly higher endemicity which is mainly due to climatic factors. These regions are located in the northern part of the country (Gabrovo, Razgrad, Targovishte, Montana, and Dobrich). In

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northern Bulgaria with especially humid spring and summer months, the rainfall maximum is during the month of June [10]. Data on the seasonal distribution of cases of LB in our country showed a peak in seasonal activity of the tick Ixodes ricinus.

LB is a multisystemic infectious disease. Clinically, LB progresses through distinct stages. Early manifestations of LB include typical skin lesion - erythema migrans (EM) as a pathognomonic sign of early localized infection and/or unspecific flu-like symptoms. EM usually appears within 3 to 30 days after the tick bite in at least 80% of patients, followed by early disseminated and late stages. If left untreated, has the potential to cause long-term complications with a significantly reduced quality of life for individuals [11]. Lyme neuroborreliosis (LNB) is the most severe manifestation is LB and occurs in 10% to 15% of untreated patients [12]. Borrelia burgdorferi can affect the nervous system through diverse mechanisms, often creating considerable diagnostic challenges and clinical uncertainty [13]. Neurological disturbances can appear at any time within the disseminated stage and both the central nervous system (CNS) and peripheral nervous system (PNS) can be involved. Nervous system involvement late in the course of Lyme borreliosis is much less common than in early disseminated stage of the disease. The clinical course of LNB is highly variable, the onset is usually subacute with a progressive course.

Historically, the first case of LNB was reported by Garin and Bujadoux in 1992 when they described a patient in France with meningoradiculitis after an erythema migrans following a tick bite. Some years later, Bannwarth described in Germany a series of patients with a similar disorder, which was recognized in Europe as Garin–Bujadoux–Bannwarth or Bannwarth syndrome (BS) [14].

Bannwarth's syndrome (meningoradiculoneuritis) is the hallmark of European early Lyme neuroborreliosis (E-LNB) and is rarely seen in North American LNB (NA-LNB). BS typically appears the classic triad lymphocytic meningitis, radiculoneuritis (sensory or motor or both) and cranial neuropathy (primarily isolated facial palsy) [15]. The onset of symptoms can vary from weeks to months after exposure. The course of borrelial meningitis in adult European patients clinically it manifests with intermittent headache. Patients with BS usually have severe, migrating radicular pain that can be accompanied by peripheral nerve paresis, often combined with uni- or bilateral (one-third of cases) facial palsy and CSF pleocytosis with lymphocytic predominance. American Lyme neuroborreliosis almost always presents as subacute meningitis with or without associated cranial neuropathy (usually facial palsy). Late complications of LNB such as encephalitis and myelitis are exceptionally rare. Cognitive and memory impairment is characterized by impaired concentration and memory. It progresses slowly and may be accompanied by diffuse polyneuropathy.

Except for EM, disease expressions are not specific and need laboratory confirmation. For patients with an EM > 5 cm in an endemic area with a history of tick exposure, a clinical diagnosis is sufficient [16]. Testing is not indicated in these patients, and the serologic tests would likely be negative due to lack of antibody development in early disease. For patients with early LD presenting without EM, diagnosis is incredibly challenging [17]. Whereas most patients with EM are seronegative, most patients with neuroborreliosis should be seropositive.

The serological diagnosis should follow a two-tier testing protocol involving a sensitive enzyme immunoassay analysis (EIA) as the first step (screening test), followed by immunoblot (IgM and IgG). Seroconversion to IgG typically occurs within 6 weeks. The late immune responses in Lyme disease are mediated by IgG against the VlsE antigen, detectable in more than 90% of positive sera [18]. IgG can remain positive for many years after recovery.

LNB remains a diagnostic challenge due to its various presentations. A reliable diagnosis of neuroborreliosis is based on epidemiological history (tick exposure), clinical suspicion (neurological symptoms), cerebrospinal fluid analysis (lymphocytic pleocytosis) and the detection of antibodies against Borrelia in serum and CSF, especially an intrathecal synthesis of Borrelia specific antibodies in CSF [19]. Laboratory confirmation of LNB (isolation of Borrelia from the CSF) is hampered by the low sensitivity of polymerase chain reaction (PCR) in CSF, around 40% [20,21]. In addition, the demonstration of intrathecal synthesis of antibodies against B. burgdorferi in the CSF has been considered a gold standard for the diagnosis of CNS infection in Europe, where B. garinii is the species most often associated with LNB. Evidence of intrathecal antibody production has been found in approximately 90% of patients with acute neuroborreliosis. Intrathecal production may persist for a long time after successful therapy. The CXCL13 is a promising unspecific biomarker for the detection of intrathecal inflammation, especially in early LNB. CXCL13 levels decrease significantly after antibiotic treatment, making it a possible marker for disease activity and treatment control [22].

The recommendations from Europe and North America are quite homogeneous regarding on the clinical presentations and diagnostic methods of Lyme disease. The European Federation of Neurological Societies (EFNS), the American Academy of Neurology (AAN), and the Infectious Diseases Society of America (IDSA) have all recommended specific criteria for the diagnosis of LNB. The European diagnostic criteria of LNB recommend CSF analysis for intrathecal

antibody production detection and comparing CSF and serum antibody rates [23]. The intrathecal anti-Borrelia antibody index is a necessary criterion to diagnose neuroborreliosis in Europe, but not in the USA [24].

Computed tomography (CT) scans of patients who developed nervous system involvement are usually normal. Reported CT abnormalities have included focal or multifocal areas of low density in the subcortical and/or periventricular white matter. Due to its sensitivity and specificity, magnetic resonance imaging (MRI) may be perceived as preferable to CT regarding examination of lesions in the course of LNB. MRI offers higher anatomical resolution, better soft tissue contrast, and multiplanar imaging acquisition [25]. Patients with longer duration of symptoms are more likely to have LNB findings on MRI [26].

Treatment with an appropriate course of antibiotics leads to robust improvement in neurological symptoms [27]. Currently, the antibiotic treatment most often used for patients with LNB is a 2-week for early LNB (duration <6 months) or 3-week for late LNB (duration >6 months) course of antibiotic therapy, usually with intravenous ceftriaxone at a dosage of 2 g daily [28]. Treatment efficacy is detected by the improvement of the neurological symptoms and the normalization of the CSF pleocytosis.

2. Conclusion

Lyme disease is the most commonly reported vectorborne disease in the northern hemisphere. Following the description of the disease in Connecticut (USA) and the discovery of its agent in the 1980s, most aspects of of Lyme borreliosis are well known. LB can present with neurological symptoms such as neuroborreliosis (LNB) with both the peripheral and central nervous systems involvement. The clinical course of LNB is highly variable. In Europe 70% of patients with early LNB develop Bannwarth syndrome, including lymphocytic meningitis, cranial nerve palsies, or radiculoneuritis that may occur individually or in combination. Myelitis and encephalitis are rare manifestation of late LNB. The diagnostic process, may be challenging in clinical practice. Antibiotic treatment prevents disease progression.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest is disclosed by the authors.

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