Lyme Borreliosis - a Multisystem Disease

Angela Revelas[1], Emmanuel Liannos[2], Dimitrios Arvanitakis[3]
[1]*Pathological Department of St.Nicolaos-Crete, Greece*
[2]*Urological Department of St.Nicolaos-Crete, Greece*
[3]*Neurosurgery Clinic of Venizeleio General Hospital-Crete, Greece*

Corresponding Author
Dr.Angela Revelas

Mobile:
6943503095

E mail:
donnoiko@gmail.com

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Lyme borreliosis, due to the tick-borne spirochete *Borrelia burgdorferi sensu lato* (Bb.sl), causes significant morbidity throughout the world. Preliminary studies have indicated the presence of the arthropod vector and the pathogen in North Africa. A few clinical cases have been reported. Our objective is to evaluate whether Lyme borreliosis constitutes a threat to public health. To access our objective, we plan to establish a map of the tick distribution, to evaluate the prevalence of Borrelia infection in ticks, to identify Borrelia strains and to determine their genetic diversity, to identify reservoirs used to maintain Bb.sl, and to evaluate the incidence of the disease in the human population. The knowledge of the natural enzootic cycle involving arthropods and wild vertebrates in the maintenance of Bb.sl should permit to develop prevention strategies to counter any public health threat.

INTRODUCTION

Lyme borreliosis is a multisystem disease involving the skin, nervous system, joints and heart [1]. The causative agent *Borrelia burgdorferi* is transmitted by tick bite [2]. The prevalence of specific antibodies of blood donors living in endemic areas as described in south Lower Saxony (Germany) has been 7% and of forestry workers 21%, indicating that this is the most prevalent arthropod-borne infection in this geographic region [3,4]. One third of flagged Ixodes ricinus contain *B.burgdorferi* as demonstrated by polymerase chain reaction (PCR) [5]. Therefore reinfection should not be a rare event. Forestry workers with a high risk of repeated tick bites often have a high prevalence and high titers of specific antibodies but only sporadic corresponding clinical symptoms of Lyme borreliosis [6-8]. Thus it has been concluded that a natural protection existed in most cases after an infection with the spirochete.

HISTORY

In 1980, Steere et al., began to test antibiotic regimens in adult patients with Lyme disease [9]. In the same year, New York State Health Dept. epidemiologist Jorge Benach provided Willy Burgdorfer, a researcher at the Rocky Mountain Biological Laboratory, with collections of *I. dammini* from Shelter Island, NY, a known Lyme-endemic area as part of an ongoing investigation of Rocky Mountain spotted fever. In examining the ticks for rickettsiae, Burgdorfer noticed 'poorly stained, rather long, irregularly coiled spirochetes'. Further examination revealed spirochetes in 60% of the ticks. Burgdorfer subsequently confirmed his discovery by isolating from patients with Lyme disease spirochetes identical to those found in ticks [10]. In June 1982, he published his findings in Science, and the spirochete was named *Borrelia burgdorferi* in his honor [2].

PATHOPHYSIOLOGY

Borrelia burgdorferi can spread throughout the body during the course of the disease, and has been found in the skin, heart, joint, peripheral nervous system and central nervous system. Many of the signs and symptoms of Lyme disease are a

consequence of the immune response to the spirochete in those tissues [11]. *B.burgdorferi* is injected into the skin by the bite of an infected Ixodes tick. Tick saliva, which accompanies the spirochete into the skin during the feeding process, contains substances that disrupt the immune response at the site of the bite [12]. This provides a protective environment where the spirochete can establish infection. The spirochetes multiply and migrate outward within the dermis. Days to weeks following the tick bite, the spirochetes spread via the blood stream to joints, heart, nervous system, and distant skin sites, where their presence gives rise to the variety of symptoms of disseminated disease. The spread of *B.burgdorferi* is aided by the attachment of the host protease plasmin to the surface of the spirochete. If untreated, the bacteria may persist in the body for months or even years, despite the production of *B.burgdorferi* antibodies by the immune system. In the brain, *B.burgdorferi* may induce astrocytes to undergo astrogliosis, which may contribute to neurodysfunction [13]. The spirochetes may also induce host cells to secrete products toxic to nerve cells, including quinolinic acid and the cytokines IL-6 and TNF-alpha, which can produce fatigue and malaise [14,15].

In Lyme encephalopathy, diffuse white matter pathology can disrupt grey matter connections, and could account for deficits in attention, memory, visuospatial ability, complex cognition, and emotional status. White matter disease may have a greater potential for recovery than gray matter disease, perhaps because neuronal loss is less common.

EPIDEMIOLOGY

In northern Africa, *B.burgdorferi* sensu lato has been identified in Morocco,Algeria, Egypt and Tunisia [16-18]. Lyme disease in Sub-Saharan Africa is presently unknown, but evidence indicates it may occur in humans in this region. The abundance of hosts and tick vectors would favor the establishment of Lyme infection in Africa. In East Africa, two cases of Lyme disease have been reported in Kenya [19].

SIGNS AND SYMPTOMS

Lyme disease can affect multiple body systems and produce a range of symptoms. Not all patients with Lyme disease will have all symptoms, and many of the symptoms are not specific to Lyme disease, but can occur with other diseases as well. The incubation period from infection to the onset of symptoms is usually one to two weeks, but can be much shorter, or much longer. Symptoms most often occur from May through September, because the nymphal stage of the tick is responsible for most cases. Asymptomatic infection may be much more common among those infected in Europe.

DIAGNOSIS

Patients with *B. burgdorferi* sensu lato infection may experience one or more clinical syndromes of early or late LB. Usually, early infection consists of localized erythema migrans (EM), which may be followed within days or weeks by clinical evidence of disseminated infection that may affect the skin, nervous system, heart, or joints and subsequently, within months, by late infection [20-23]. EM is the characteristic sign of early infection with *B. burgdorferi* sensu lato and the clinical hallmark of LB. In recent series it is recognized in at least 80% of patients with objective clinical evidence of *B. burgdorferi* sensu lato infection who meet the CDC surveillance definition of LB [24]. The rash begins at the site of the tick bite as a red macule or papule, rapidly enlarges, and sometimes develops central clearing. The clinical diagnosis of early LB with EM relies on recognition of the characteristic appearance of a skin lesion of at least 5 cm in diameter. Hematogenous dissemination of *B. burgdorferi* sensu lato to the nervous system, joints, heart, or other skin areas, and occasionally to other organs, may give rise to a wide spectrum of clinical manifestations of what is called early LB. Usually, patients with objective evidence of dissemination experience one or more of the following syndromes: multiple EM lesions, atrioventricular conduction defects, myopericarditis, arthritis, facial palsy, meningitis, and meningoradiculoneuritis (Bannwarth's syndrome) [25-27].

Labotary Diagnosis

A variety of laboratory techniques have been developed for direct detection of *B. burgdorferi* sensu lato. These assays provide evidence for the presence of intact spirochetes or spirochete components such as DNA or protein in tick vectors, reservoir hosts, or patients.

Four different approaches have been used in the clinical laboratory: microscope-based assays, detection of *B. burgdorferi*-specific proteins or nucleic acids, and culture. Of these, culture of *B.*

burgdorferi sensu lato undoubtedly offers the best confirmation of active infection and has been increasingly used as a diagnostic modality by many researchers on both sides of the Atlantic. The availability of cultured organisms has also allowed investigation of the structural, molecular, antigenic, and pathogenetic properties of the different *B. burgdorferi* sensu lato species.

Direct microscopic detection of *B. burgdorferi* sensu lato has limited clinical utility in laboratory confirmation of LB due to the sparseness of organisms in clinical samples [28-33] Antigen detection assays (aside from PCR) also suffer from the same limitations as microscopic detection. Although antigen capture tests have been used to detect *B. burgdorferi* sensu lato antigens in CSF of patients with neuroborreliosis [34,35] and in urine samples from patients with suspected LB [36], their reliability is poor or at best questionable [37].

Prevention of tick bites

The ticks that can transmit Lyme disease are found in wooded areas, high grasses, marshes, gardens, and beach areas. In endemic residential areas, clearing brush and trees, removing leaf litter and woodpiles, and keeping grass mowed may reduce tick exposure by removing habitats suitable for ticks and their reservoir hosts [38]. Area application of pesticides to residential properties is effective for suppressing vector ticks but may be harmful to other wildlife and people [39]. Exclusion of deer from residential yards by fencing and maintaining tick-free pets also may reduce tick exposure [40]. Heavily infested tick habitats, such as wooded areas, should be avoided if possible. If not possible, then use of wide trails, not straying off the trail, and not sitting on the ground may decrease exposure. Careful attention also should be given to clothing worn in these areas. Clothing should be light-colored to make tick identification easier. Long sleeves and long pants that are tight at the wrists, ankles, and waist, and long pants tucked into light colored socks are preferable. A hat should be worn in densely wooded areas. Persons should be taught to inspect themselves and their children's bodies and clothing daily after possible tick exposure. Special attention should be given to the exposed hairy regions of the body where ticks often attach, including the heads and necks of children.

Because animal studies indicate that transmission of *B. burgdorferi* from infected ticks usually requires a prolonged duration of attachment (≥48 hours), ticks should be removed promptly [41,42]. The body of the tick should not be squeezed during removal. It should be grasped with a fine tweezers as close to the skin as possible and removed by gently pulling the tick straight out without twisting motions. If fingers are used to remove ticks, they should be protected with gloves or facial tissue and washed after removal of the tick. Analysis of ticks to determine if they are infected is not indicated because the predictive values of such tests in relation to the development of human disease are unknown.

NEUROLOGIC MANIFESTATIONS

Myositis is rare and may occur in the early or late stage. It is diagnosed by muscle enzymes, electromyography or biopsy. Myositis is associated with pains and paresis in proximal muscles in particular. Neuritis cranialis is an acute manifestation and may affect all the cranial nerves including the N. olfactorius. Unilateral or bilateral paresis may occur and recur. Mono-or polyradiculitis and meningopolyradiculitis are the neurologic symptoms of borreliosis that occur most frequently, corresponding to the descriptions by Garin, Bujadoux and Bannwarth [3,4]. Radiculitis is connected to an elevated protein concentration , and meningitis is accompanied by lymphocystic pleocytosis.

PROGNOSIS

For early cases, prompt treatment is usually curative. However, the severity and treatment of Lyme disease may be complicated due to late diagnosis, failure of antibiotic treatment, and simultaneous infection with other tick-borne diseases, including ehrlichiosis, babesiosis, and immune suppression in the patient. A meta-analysis published in 2005 found some patients with Lyme disease have fatigue, joint or muscle pain, and neurocognitive symptoms persisting for years, despite antibiotic treatment [7]. Patients with late stage Lyme disease have been shown to experience a level of physical disability equivalent to that seen in congestive heart failure.

Lyme Disease Vaccine

Animal studies have demonstrated that purified recombinant proteins, particularly of certain outer surface proteins (Osp) of *B burgdorferi,*

such as Osp A, B, and C, induce antibody responses that are highly protective [43]. The most extensively studied [44] of the single Osp vaccines and the one currently licensed contains recombinant OspA (rOspA), which is highly protective in the mouse model when the challenge strain is homologous or closely related to the isolate from which the OspA was derived [45,46]. However, when the challenge strain is different from the isolate from which the OspA was derived, protection to challenge is minimal or nonexistent.

Route of administration, immunization schedule, and dose:

Three doses of 0.5 mL (30 μg) of rOspA vaccine administered by intramuscular injection are required for optimal protection; the second dose is given 1 month later, and a third dose is given 12 months after the first dose. Dosages should be timed so that the second and the third doses are given several weeks before the start of the Lyme disease transmission season, which usually begins in April.

Preliminary data suggest that other immunization schedules (e.g., 0, 1, 6 months) are safe and induce antibody responses similar to the 0, 1, 12 month schedule [46]. However, at this time, only the 0, 1, 12 month schedule is approved by the US Food and Drug Administration.

CONCLUSION

Borrelia is transmitted to humans by the bite of infected ticks belonging to a few species of the genus Ixodes. Delayed or inadequate treatment can lead to the more serious symptoms, which can be disabling and difficult to treat. At present the major problem in the early diagnosis of borreliosis is the high percentage of seronegativity of 20-50% depending on the duration of the erythema migrans. Another problem is the persistence of elevated IgM antibodies after therapy. Misinterpretations of serology contribute to the over diagnosis and over treatment of chronic Lyme disease and irrational Lyme anxiety. The diagnosis of Lyme borreliosis should primarily be based on clinical and epidemiologic evidence.

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Peer Reviewer: Mohamad Emara ;Lecturer of Tropical Medicine, Zagazig University, Egypt. **Editor :Tarik Zaher**; Assistant Professor of Tropical Medicine, Zagazig University, Egypt