Epidemiology of Lyme Neuroborreliosis

David S. Younger, MD, MPH, MS[a,b,*]

KEYWORDS

• Lyme disease • *Borrelia burgdorferi* • Neurology • Public health • Epidemiology

KEY POINTS

- According to the Centers for Disease Control and Prevention, Lyme disease is the most commonly reported vector-borne illness and the fifth most common disease in the National Notifiable Diseases Surveillance System, making it an important public health concern.
- Lyme disease is caused by the bacterium *Borrelia burgdorferi* and is transmitted to humans through the bite of infected blacklegged *Ixodes* ticks.
- Typical symptoms include fever, headache, fatigue, and a characteristic skin rash called *erythema migrans*.
- Undiagnosed and therefore untreated, infection disseminates to the nervous system.
- The nonhuman primate model of Lyme neuroborreliosis accurately mimicked the microbiological, clinical, immunologic, and neuropathologic aspects of human Lyme neuroborreliosis.

INTRODUCTION

Lyme disease in humans is caused by the transmission of *Borrelia (B) burgdorferi* in the bite of infected blacklegged *Ixodes* ticks. Typical symptoms include fever, headache, fatigue, and a characteristic skin rash called *erythema migrans* (EM). If left undiagnosed and therefore untreated, infection disseminates to the nervous system causing Lyme neuroborreliosis (LNB). The clinical diagnosis is based on symptoms, physical findings, and the probability of exposure to infected ticks in endemic geographic areas and confirmed by serologic and cerebrospinal fluid (CSF) testing with the demonstration of intrathecal production of *Borrelia*-specific antibodies. There is general recognition for the potential of infectious-related autoimmune processes contributing to nervous system disease progression.

The author has nothing to disclose.

[a] Division of Neuroepidemiology, Department of Neurology, New York University School of Medicine, New York, NY, USA; [b] College of Global Public Health, New York University, New York, NY, USA

* Corresponding author. 333 East 34th Street, 1J, New York, NY 10016.

E-mail address: david.younger@nyumc.org

Neurol Clin 34 (2016) 875–886

http://dx.doi.org/10.1016/j.ncl.2016.05.005 **neurologic.theclinics.com**

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HISTORY

Originally named for Lyme and Old Lyme, Connecticut, wherein a tight clustering of recurrent attacks of childhood and adult asymmetric oligoarticular arthralgia occurred beginning in 1972, Lyme disease showed a peak incidence of new cases in the summer and early fall.[1,2] Epidemiologic analysis of the clustering suggested transmission of a causative agent by an arthropod vector to humans, in whom 25% describe an expanding annular EM rash before onset of the arthritis. Cultures of the synovium and synovial fluid did not suggest infection with agents known to cause other forms of arthritis. Those in whom arthritis developed seemed to have significantly elevated ESR, lower third and fourth components of complement (C3, C4), higher serum IgM levels, and serum cryoprecipitates at the time of the skin lesions, suggesting an active immunologic response. Five years later, Burgdorfer and colleagues[3] isolated a spirochete from the tick *Ixodes (I) dammini* that bound immunoglobulins of patients convalescing from Lyme disease and recorded the development of lesions resembling EM in New Zealand white rabbits 10 to 12 weeks after being bitten by the ticks. One year later in the same volume of *The New England Journal of Medicine*, Steere and coworkers[4] and Benach and colleagues[5] described the spirochetal etiology of Lyme disease. Benach and colleagues[4] isolated spirochetes from the blood of 2 of 36 patients in Long Island and Westchester County, New York with signs and symptoms suggestive of Lyme disease that were morphologically similar and serologically identical to organisms known to infect *I dammini* ticks, endemic to the area and epidemiologically implicated as vectors of Lyme disease.

CLINICAL INVOLVEMENT

By 1989 Steere[6] summarized the causation, vector and animal hosts, clinical manifestations, pathogenesis, and treatment of human Lyme disease. Three stages of infection were recognized, each with different clinical manifestations. Stage 1 followed the bite by the tick with spread of bacteria locally in the skin in 60% to 80% of patients, resulting in EM rash that faded in 3 to 4 weeks but often accompanied by fever, minor constitutional symptoms, or regional adenopathy. At this time, the patient's mononuclear cells responded minimally to spirochete antigens, and even specific antibody might be lacking. Stage 2 of early infection followed days or weeks after the bite with bloodstream or lymphatic spread to many organ sites. More common in the United States than in Europe, widespread dissemination resulted in recovery of spirochete from tissue specimens of meninges, brain, myocardium, retina, muscle, bone, synovium, spleen, and liver.[7]

NONHUMAN PRIMATE STUDIES

Between 1998 and 1993 two animal models, a murine[8] and nonhuman primate (NHP)[9,10] accurately mimicked the microbiological, clinical, immunologic, and neuropathologic aspects of LNB. Two methods of spirochete inoculation, by needle injection of 1 million N40Br strain spirochetes and feeding of infected ticks were found to be comparable in establishing infection. Transient immunosuppression maximized the yield of infection in some of the NHPs. The central nervous system (CNS) was a major reservoir of spirochetal infection and showed that a strong, well-developed anti-*Borrelia* humoral immune response did not clear spirochetes from NHP during the months of infection. Accordingly, spirochetal presence was a necessary but not sufficient condition for inflammation.

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