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Brazilian borreliosis with special emphasis on humans and horses

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ABSTRACT

Borreliosis caused by *Borrelia burgdorferi* sensu lato is a cosmopolitan zoonosis studied worldwide; it is called Lyme disease in many countries of the Northern Hemisphere and Lyme-like or Baggio-Yoshinari Syndrome in Brazil. However, despite the increasing number of suspect cases, this disease is still neglected in Brazil by the medical and veterinary communities. Brazilian Lyme-like borreliosis likely involves capybaras as reservoirs and *Amblyomma* and *Rhipicephalus* ticks as vectors. Thus, domestic animals can serve as key carriers in pathogen dissemination. This zoonosis has been little studied in horses in Brazil. The first survey was performed in the state of Rio de Janeiro, and this Brazilian Borreliosis exhibits many differences from the disease widely described in the Northern Hemisphere. The etiological agent shows different morphological and genetic characteristics, the disease has a higher recurrence rate after treatment with antibiotics, and the pathogen stimulates intense symptoms such as a broader immune response in humans. Additionally, the Brazilian zoonosis is not transmitted by the *Ixodes ricinus* complex. With respect to clinical manifestations, Baggio-Yoshinari Syndrome has been reported to cause neurological, cardiac, ophthalmic, muscle, and joint alterations in humans. These symptoms can possibly occur in horses. Here, we present a current panel of studies involving the disease in humans and equines, particularly in Brazil.

Lyme disease (LD) or Lyme borreliosis (LB) is the most common tick-borne disease in temperate regions of the Northern Hemisphere and is caused by the spirochete *Borrelia burgdorferi* sensu lato.[1] LD is a multistage disease that can affect multiple organs but in humans manifests predominantly in the skin, joints, and nervous system.[2]

History

In 1976, children in a geographical region of the United States, specifically near the town of Lyme, Connecticut, were affected by a mysterious syndrome[3] that was initially diagnosed as

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juvenile rheumatoid arthritis.[1] In 1981, the entomologist and physician Willy Burgdorfer, along with Alan Barbour and Jorge Benach, found a spirochete in the midgut of ticks of the genus *Ixodes* in an area of New York, a known endemic focus of LD. The researchers cultivated samples from ticks in a culture medium developed for growing the relapsing fever spirochete (*B. hermisii*) and found a new species of *Borrelia*, subsequently named *B. burgdorferi*.[4] Later, the same bacterium was isolated and cultivated from the blood of patients with LD.

The diseases termed Lyme borrelioses are known to be caused by a large number of species related to *B. burgdorferi*, which are called *B. burgdorferi* sensu lato.[5] Of the 34 existing *Borrelia* spp., 20 are referred to as *Borrelia burgdorferi* sensu lato and cause LD, which is transmitted by ticks of the genus *Ixodes*. Of these 20 species, only nine have been isolated from humans in the Northern Hemisphere (*B. afzelii*, *B. bavariensis*, *B. bissetti*, *B. burgdorferi* stricto sensu, *B. garinii*, *B. kurtenbachii*, *B. lusitaniae*, *B. spielmanii*, and *B. valaisiana*).[6]

The first isolation of *B. burgdorferi* sensu lato in the Southern Hemisphere was performed by Barbieri et al. in Uruguay from *I. pararicinus* ticks. Thereafter, the bacterium was also identified in Argentina[7] and Chile,[8,9] where it was named *B. chilensis*. All three isolations revealed the bacterium in ticks of the *I. ricinus* complex using amplification of the 16S ribosomal gene, 5S-23S intergenic spacer, and flagellin gene (*fla*) for species identification.

B. burgdorferi sensu lato is a highly invasive gram-negative spirochete. Its pathogenicity depends on its mobility, cytotoxicity, antigenic variability, lymphocyte stimulation, and resistance to complement activation in the absence of specific antibodies.[10]

Transmission

The pathogen is mainly transmitted by ticks of the *I. ricinus* complex.[11] However, there are reports of *B. burgdorferi* s.l. transmission by *Amblyomma americanum* in Florida and Georgia in the United States.[12] It has also been identified in *Dermacentor nitens* in the state of Paraná, Brazil.[13]

The bacteria can infect the tick when it feeds on an infected reservoir host.[11] After molting to the nymph stage, the ticks are able to transmit the pathogen to the animal from which it obtains its next blood meal. As transtadial transmission is not always successful, transmission of the bacteria is ensured by an enzootic cycle in which the tick feeds on various vertebrate hosts.[14]

The spirochetes are deposited into the bite wound along with the tick saliva. For infection to succeed, the tick must feed for at least 24 h adhered to the host, a period after which there is reduced expression of Outer Surface Proteins A and B (OspA and OspB) and increased expression of Outer Surface Protein C (OspC). OspAs and OspBs are lipoproteins essential for the survival of Borrelia spp. in the tick midgut. OspC is crucial for establishing infection in the invertebrate host because the protein allows the bacteria to migrate from the tick midgut to the salivary glands, where they will be carried with the saliva to the vertebrate host.[15] OspC also has an important role in the vertebrate host because it induces immunosuppression, thereby favoring infection.[14] Tilly and co-workers[16] found that bacteria lacking OspC do not establish infection in mice by either bacterial inoculation via injection or by tick bite.

Immune response

In the vertebrate host, *Borrelia* spp. are recognized by several mechanisms of the immune response, including the complement system and diverse innate immune cells.[17] Despite being classified as gram negative, *B. burgdorferi* does not produce lipopolysaccharide (LPS) but does express OspC in vertebrates. Recognition of *Borrelia* spp. by dendritic cells leads to maturation of these cells and triggers transcription of a large set of genes, such as those expressing chemokines, apoptosis inhibitors, matrix metalloproteases and a large subset of cytokines, including proinflammatory mediators, neutrophils attractants, immunomodulatory cytokines.[18]

Following antigen presentation by dendritic cells, T_H1 and T_H2 lymphocyte helper T cells initiate the adaptive response, promoting the release of interferon IFN-γ and interleukin IL-4, which are directly related to the severity of acute symptoms.[17] Subsequently, the cytokines released by T_H cells induce B-lymphocyte proliferation of and consequently, immunoglobulin production.[18]

Although the immune system attempts to prevent *Borrelia* infection, the spirochete has its own mechanisms to avoid host defenses. Components of the tick's saliva (such as *Salp*15) are known to be able to suppress the dendritic cell response, increasing the pathogenic virulence of *Borrelia*.[17] The spirochetes can also inactivate the host complement system by binding to host complement regulatory proteins, thereby inactivating the C3b mechanism. Another mechanism employed by *Borrelia* to escape the immune response is antigenic variation. The variable major protein-like sequence gene locus (*vls*E) on plasmid 28-1 undergoes extensive variation, which is stimulated by tick feeding.[18]

The disease in humans (LD of the Northern Hemisphere versus Brazilian Baggio-Yoshinari Syndrome)

Acute LD is typically manifested by an expanding erythematous skin lesion. Late manifestations may include arthritis, acrodermatitis chronica atrophicans, lymphocytoma, myocarditis, conjunctivitis, uveitis, and neurological signs.[19]

The existence of borreliosis in humans in Brazil was first suggested by Dr. Yoshinari and co-workers[20]; however, the first case in the country was not diagnosed until 1992. The increasing number of cases identified in Brazil show differences from the disease that occurs in the Northern Hemisphere.[21–24] In Brazil, the occurrence of *Ixodes* ticks (*I. auritulus* and *I. loricatus*) is associated with parasitism of some birds and *Didelphis albiventris*,[25,26] which are not considered the preferential vectors for horses and humans. Clinically, despite the occurrence of signs such as erythema migrans and the usual systemic complications, the Brazilian disease progresses with recurrences, especially if antibiotic treatment is initiated later than three months after infection. Brazilian patients

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