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Borrelia Infection in Latin America

Alejandro Robles[1], James Fong[2] and Jorge Cervantes[2,3]*

[1]Department of Internal Medicine, [2]Paul L. Foster School of Medicine and [3]Department of Medical Education, Texas Tech University Health Sciences Center, El Paso, TX, USA

ABSTRACT

Lyme disease (LD) is a multisystemic inflammatory disease caused by pathogenic spirochetes, belonging to the genospecies complex *Borrelia burgdorferi* sensu lato (B.b.s.l.). Around the world, distinct species of *Ixodes* tick vectors transmit different species of *Borrelia*. Despite the rising recognition and occurrence of tick-borne disease in Latin America, serology has proven to be inconclusive in detecting suspected LD cases. Recently, new B.b.s.l. strains or new related species have been described in Brazil, Uruguay, and Chile. This could explain the lack of confirmatory tests, such as indeterminate Western blots (WBs) and polymerase chain reactions, in detecting suspected LD cases in this region of the world. Future studies will need to determine the extension of novel B.b.s.l. species infections in ticks, reservoirs, and humans in Latin America. The existence of these new *Borrelia* genomic species should prompt the development of innovative diagnostic and clinical approaches. (REV INVES CLIN. 2018;70:158-63)

Key words: Lyme disease. *Borrelia*. Latin America.

LYME DISEASE (LD) - GLOBAL DISTRIBUTION

LD is the most common vector-borne illness in the United States, and a major zoonosis in Europe and China[1,2]. It is currently the zoonosis transmitted by arthropods with the highest incidence rate and prevalence in the United States, Europe, and Asia. LD is a multisystemic inflammatory disease caused by pathogenic spirochetes of the *Borrelia burgdorferi* sensu lato (B.b.s.l.) complex.

LD was first described nearly 40 years ago after an investigation of a cluster of cases originally thought to be juvenile rheumatoid arthritis in children living in Connecticut[3]. However, there is evidence to suggest

Corresponding author:
*Jorge Cervantes
Department of Medical Education
Paul L. Foster School of Medicine
Texas Tech University Health Sciences Center
5001 El Paso Dr., El Paso, TX, 79905, USA
E-mail: jorge.cervantes@ttuhsc.edu

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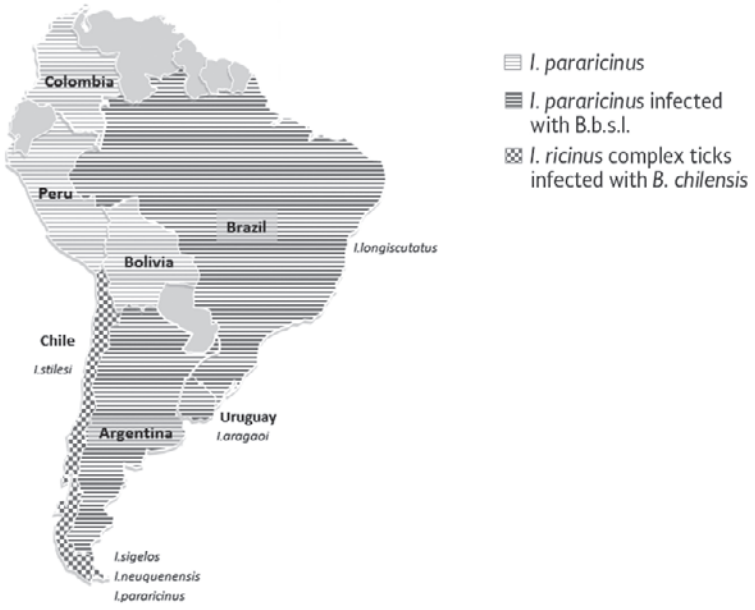
Figure 1. Presence of *Borrelia burgdorferi* sensu lato in ticks from South America.



that B.b. has affected humans for thousands of years. The Tyrolean Iceman, or Ötzi, a 5300-year-old mummy discovered in 1991 in the Ötztal Alps, has become one of the most studied cadavers in science. A whole-genome study was performed in 2010 yielding, among other things, sequences corresponding to approximately 60% of the genome of B.b., making him the earliest known human to be infected by the pathogen that causes LD[4]. The finding of multiple simple linear tattoos at or near traditional acupuncture points, along with the presence of B.b. DNA makes a compelling case that this individual was possibly affected by LD[5].

Although originally described in North America, borreliosis has also been described in other parts of the world such as Asia, Russia, North Africa, and Europe[2,6], and possibly Oceania[7] and South America[8]. The spirochetes are transmitted to humans when accidentally bitten by ticks infected with the pathogen.

VECTORS AND *BORRELIA* EVOLUTION

The species of *Borrelia* associated with LD are grouped in a bacterial genospecies complex called B.b.s.l., which includes *B. burgdorferi* sensu stricto (B.b.s.s)[9]. In Eurasia, other five genospecies of the B.b.s.l. complex are associated with LD: B.b , *Borrelia afzelii, Borrelia garinii, Borrelia bavariensis, and Borrelia spielmanii*[9,10]. These species, transmitted through geographically diverse tick vectors, are associated with different clinical presentations of the disease[11]. This *Borrelia* and tick specificity also holds true for *Borrelia* that causes relapsing fever[12] and has been confirmed in several parts around the world, including Russia and Asia[13-15].

In the United States, the LD spirochete lives in nature in an enzootic cycle that includes mainly ticks of the genus *Ixodes*[2]. *Ixodes scapularis* was initially implicated as a vector in the southeastern United States and has expanded throughout the decades[16,17]. Currently, in North America, B.b is mostly transmitted by *I. scapularis* ticks in northeastern and Midwestern United States and South Canada, and by *Ixodes pacificus* in the West Coast of the United States and Canada. In Eurasia, the different B.b.s.l. genospecies use *Ixodes ricinus* (in Europe) and *Ixodes persulcatus* (in Asia) for transmission[10]. The rodent *Peromyscus leucopus* is the main reservoir of the disease, and the white-tailed deer (*Odocoileus virginianus*) serves as the tick's primary host.

The Neotropical tick *Ixodes pararicinus* is distributed along Argentina, Colombia, and Uruguay, but it is also probably established in Bolivia, Brazil, Chile, and Peru[18] (Fig. 1). Bird migration appears to help in the dispersion of infected ticks across countries[19]. Most adult ticks of this species have been found on introduced domestic artiodactyls, although Neotropical deer species must have been the ancestral host[20]. Larvae and nymphs of *I. pararicinus* have also been found on sigmodontine rodents and passeriform birds[18]. Birds from that region also harbor ticks other than the family Ixodidae such as *Haemaphysalis juxtakochi* and *Amblyomma species*[21]. There are several species of *Amblyomma* in the South American region, some of them parasitizing humans[22]. Although *I. pararicinus* is a member of the *I. ricinus* complex, which contains the main vectors of B.b.s.l., there are few studies concerning its potential for pathogen transmission in South America[23,24].

Several species of ticks of the genera *Ixodes* (*I. ricinus, I. uriae, I. chilensis, I. taglei, I. stilesie, I. sigelos, I. auritulus,* and *I. cornuae*) and Amblyomma (*A. tigrinum* and *A. maculatum*) have been described in Chile[25,26], Peru[27-29], and Argentina[23]. In the latter, two out of 12 *I. pararicinus* ticks were infected with B.b.s.l.[23]. Birds, several rodent species, and lagomorphs, like the hare, have been proposed as reservoirs[25,26]. A study aiming on detecting the presence of B.b.s.s. by polymerase chain reaction (PCR) for the *ospA* gene in ticks collected from wild rodents yielded negative results[26]. These results meant that the ticks were not colonized with B.b.s.s., although the presence of other species within the B.b.s.l. complex could not be ruled out.

BORRELIOSIS IN LATIN AMERICA

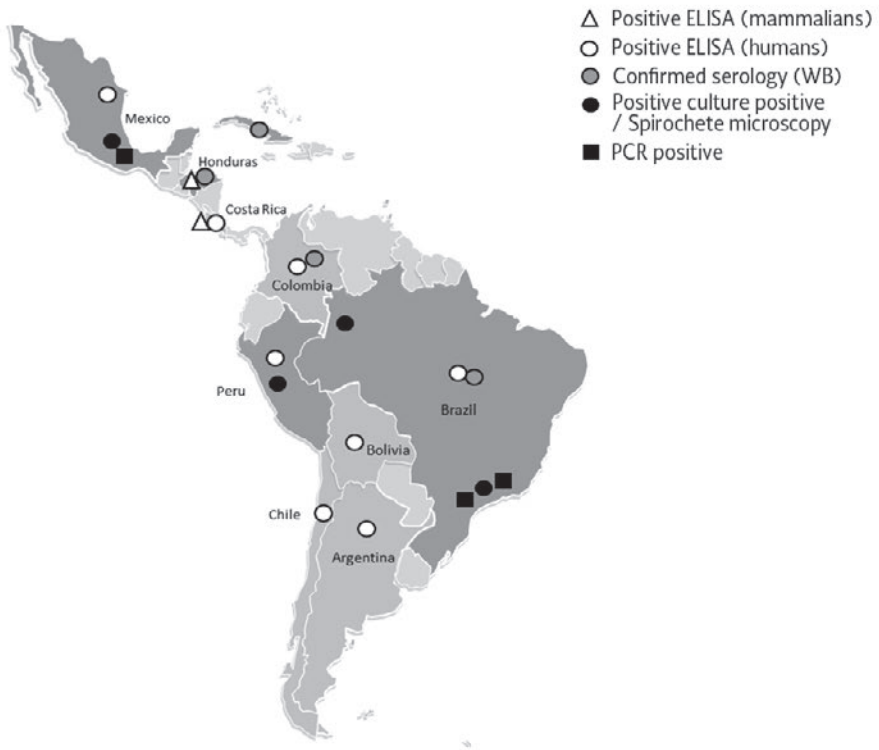
In Latin America, a national-based serosurvey in Mexico on 2980 individuals yielded a seroprevalence of 0.3% by Western blot (WB)[30]. A second study by the same group, found a seroprevalence of 3.43% in Mexico City and of 6.2% in the Northeast region of the country[31]. A later surveillance study in 72 Mexican children with clinical suspicion of LD yielded a confirmatory serology by WB in 20 of them, to three species of B.b.s.l. (*B.b.s.s., B. afzelii,* and *B. garinii*)[32]. 14 of these 20 seropositive cases rendered a positive PCR for fla and *ospA* genes in either skin, cerebrospinal fluid (CSF), or synovial fluid[32]. A case of LD with positive ELISA and confirmatory WB results was reported in Honduras in 2004[33]. In this country, a report by the U.S. Special Operations Forces on stray cats showed a prevalence of positive serology for B.b. of 25%[34]. Although B.b. was not detected in a study on dogs and cats undergoing sterilization in Costa Rica[35], two cases from this country with diagnosis based on positive IgM against B.b. have been published[36,37]. In Cuba, a serological survey using ELISA and WB rendered a seroprevalence of 2% to B.b.s.s.[38]. Serological diagnostic tests for LD have variable sensitivity and specificity, and a two-tiered serology protocol typically of an ELISA followed by a WB to detect serum IgM or IgG antibodies to B.b., is the only validated diagnostic approach for LD diagnosis[39].

In South America, tick-borne disease recognition and occurrence have been rising, due to awareness of LD, with an active search for the presence of infection by B.b. in ticks and humans. In Brazil, a Lyme-like disease known as Baggio–Yoshinari syndrome has been described since 1993[40]. This disease appears to be caused by microorganisms that may[41] or may not belong to the B.b.s.l. complex, transmitted by ticks of the Amblyomma and Rhipicephalus genera[42]. The presence of spirochetes has been detected in blood of Brazilian patients with LD-like syndrome[42], and in skin from patients with erythema migrans (EM)[43]. A study in patients with different skin disorders (distinct of LD) from Brazil showed that more than 7% of them had a positive ELISA, and over 50% of these patients had a positive WB[44]. Six cases of LD, presenting with EM, with positive ELISA serology, and one EM with direct detection of spirochetes[45], were reported between 1992 and 1999 in Peru. Cases of EM have already been documented in Peru previously[46].

A retrospective serum survey in Peru performed on 216 individuals, found 4 (2%) to be positive for B.b. antibodies by ELISA[28]. The presence of antibodies against B.b. using ELISA was found in 10% of 232 otherwise healthy subjects in Northern Peru[27]. In Colombia, the seroprevalence among farmers was 4.6%47 and 3% in Bolivia[48].

Two cases of Parry-Romberg syndrome (PRS) with positive IgM serology against B.b. were reported from Peru[49]. PRS or progressive hemifacial atrophy is a rare entity of unknown etiology, characterized by unilateral atrophy of the skin, subcutaneous tissue, and the

Figure 2. Lyme disease in Latin America.



underlying bony structures. Although no definite association between PRS and LD has been established, yet several cases have demonstrated a coincident occurrence with LD. In some instances, an IgM and positive culture of *Borrelia* have been found[49-51].

In a seroepidemiologic investigation in farm workers from Argentina with arthritis symptoms, approximately 10 % tested positive for IgM and/or IgG[52].

The first report of LD in South America came from Chile in the form of a study of 25 patients with neurological disease of unknown etiology. The study was based on clinical and serological diagnosis by ELISA, with no confirmation by isolation[53]. A later study from the same country on 118 patients with signs or symptoms suggestive of LD, added a WB to the ELISA screening. All sera and CSF were negative for confirmatory WB analysis[54]. This led toward the conclusion that there was not enough evidence to confirm the presence of the agent in the country, but from this study emerged the hypothesis of the possible existence of a local strain of Borrelia, antigenically different or with different epidemiological profiles from the one investigated in the study[54]. In Colombia, a study on 20 serum samples from patients with signs of Lyme borreliosis showed that only four fulfilled the CDC WB criteria[55]. A similar situation occurred in Brazil, where despite positive IgM serology, only one of the cases gave a positive WB, and it was undetermined in another[56]. Studies using a battery of primers to detect B.b. by PCR in Brazil, have failed, except when targeting the gene *flgE*[8]. This suggested again that a different strain of B.b. or a different species of B.b.s.l. may be the causative agent. This proved to be the case, when testing serum samples from farmers in Brazil using a nested PCR revealed the presence of *B. garinii* and B.b.s.s.[41]. A graphic summary of all the discussed reports is depicted in figure 2.

Although serology is not conclusive evidence of the presence of Lyme borreliosis in South America, it represents indirect evidence of exposure to *Borrelia*, as some cross-reactivity with other species, such as the *Borrelia* species associated with relapsing fever, may exist[57-60].

NEW *BORRELIA* SPECIES

In Uruguay, analysis of infection in ticks of the *I. ricinus* complex collected from deer, cattle, or vegetation showed that these were infected by possibly two new B.b.s.l. genospecies, one associated with *B. bissettiae* and the other phylogenetically closest to *B. americana*[61].

Although initial studies could not confirm the existence of LD in Chile, they prompt the question that a local species of *Borrelia* could be antigenically different compared to North American strains and thus did not render a positive WB[54]. A PCR-based study for the *ospA* gene of B.b.s.s. in ticks collected from wild rodents and cervidae in the Southern region of Chile, failed to detect the presence of B.b.[26]. Although the elements required for the enzootic cycle of B.b., such as the reservoir and vector, are present in Chile, their direct detection in Chilean ticks using nested PCR was negative. A new *Borrelia* species, named *B. chilensis,* has been found in *I. stilesi* ticks collected from environmental vegetation, deer, and rodents from that region[62-64]. Given the genetic differences with the American B.b. B31 strain[62], it is possible that the presence of new species could explain the lack of confirmatory tests, like WB, in previous suspected LD cases in South America. In some of the reports, there is a lack of details on the specificity of the ELISA utilized. It has been shown that even antibodies against serotypic variants of *Borrelia* species on a regional scale cannot be detected by commercial serology test kits[65].

In Southeastern US, *Borrelia* species other than B.b., such as *B. bissettiae,* have been isolated from patients with symptoms not typical of LD[66]. Future studies will need to determine the prevalence of *Borrelia* infection (B.b.s.l. and *B. chilensis*) in ticks in this part of the world.

It appears that *B. chilensis* and possible new strains or new related species are extended throughout South America[67]. Utilizing a battery of PCR methods targeting the gene flagellin (*fla*) and the rrfA-rrlB intergenic spacer region, it has been shown that *I. sigelos, I. neuquenensis,* and *I. parariciNus* ticks are infected with B.b.s.l. related to *B. chilensis* in the Patagonian*68* and northwestern regions of Argentina. (Fig. 1)[23,24,69].

New species of B.b.s.l., like the one termed *Borrelia* sp. haplotype Pampa, have been described infecting *I. longiscutatus* ticks in Brazil[70]. The clinical significance of these new *Borrelia* genomic species remains to be elucidated.

Although the initial reports have been scattered, sometimes lacking detailed information on serological testing, the inconsistent confirmatory results could be explained by the presence of new species of B.b.s.l. in these countries. Future studies will need to determine the extension of new B.b.s.l. species infections in ticks, reservoirs, and humans in Latin America. The existence of these new *Borrelia* genomic species should prompt the development of novel diagnostic and clinical approaches.

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