BRAZILIAN LYME-LIKE DISEASE OR BAGGIO-YOSHINARI SYNDROME: EXOTIC AND EMERGING BRAZILIAN TICK-BORNE ZOONOSIS.

NATANALYO HAIIME YOSHINARI1*, ELENICE MANTOVANI2, VIRGINIA LUCIA NAZARIO BONOLDI3, ROBERTA GONÇALVES MARANGONI4, GIANCARLA GAUDITANO5

Research conducted at the laboratory of Investigations in Rheumatology of the Hospital das Clínicas, School of Medicine, Universidade de São Paulo (LIM-17 HCFMUSP), São Paulo, SP, Brazil

ABSTRACT

Lyme disease (LD) is a frequent zoonosis found in the Northern Hemisphere and is considered an infectious disease caused by spirochetes belonging to Borrelia burgdorferi sensu lato complex, transmitted by ticks of the Ixodes ricinus group. In 1992, the first cases resembling LD were described in Brazil in siblings who, after a tick bite episode, developed symptoms as erythema migrans, general flu-like symptoms and arthritis. Careful analysis of Brazilian LD-like illness casuistry showed that epidemiological, clinical and laboratorial features in the country were very different from those exhibited by North American and Eurasian LD patients. Human blood-suckers Ixodes ricinus complex ticks were absent at risk areas; the disease is recurrent in the country; Borrelia burgdorferi was never isolated in Brazil and specific serologic tests have shown little positivity with inconsistent results. Furthermore, peripheral blood analysis of patients on electron microscopy exhibited structures resembling Mycoplasma spp, Chlamydia spp and spirochete-like microorganisms. In fact, they were assumed to be latent forms of spirochetes (L form or cell wall deficient bacteria) adapted to survive at inhospitable conditions in vertebrate and invertebrate hosts. For these reasons, the Brazilian zoonosis was named Baggio-Yoshinari Syndrome (BYS) and defined as: “Exotic and emerging Brazilian infectious disease, transmitted by ticks not belonging to the Ixodes ricinus complex, caused by latent spirochetes with atypical morphology, which originates LD-like symptoms, except for occurrence of relapsing episodes and auto-immune disorders”.


LYME DISEASE

Lyme Disease (LD) was discovered in 1975 in the Old Lyme Community, USA, at the report of cases suggesting juvenile idiopathic arthritis, preceded by tick bite and formation of skin lesion denominated migratory erythema (ME).1 LD etiological agent was identified in 1982 by Willy Burgdorfer, thus denominated Borrelia burgdorferi.2 However, it is convenient to remember that European researchers already knew different aspects of the disease since the beginning of the 20th Century.3,4

LD is defined as zoonosis found in the USA and Eurasia, transmitted by ticks of the Ixodes ricinus complex, caused by Borrelia burgdorferi spirochetes sensu lato, constituted by B. burgdorferi sensu stricto found in the USA and Eurasia and B. garinii and B. afzelii, observed in Europe, that cause numerous systemic clinical manifestations. This etiological diversity is responsible for regional clinical and laboratorial differences, with a higher frequency of ME and articular impairment in the USA.5 There is yet a manifestation known as Masters disease or STARI (Southern Tick Associated Rash Illness),5 identified in the south of the USA, characterized by the development of rash similar to ME, in the absence of systemic symptomatology, caused by uncultivable borrelia, known as Borrelia lonestari and transmitted by Amblyomma americanum.

LD evolves in stages. In the acute phase, ME may emerge associated with symptoms compatible with influenza, such as low fever, shiverings, myalgia, arthralgia, headache, adenomegaly, and transitory elevation of hepatic enzymes. In this stage, new less expansive and disseminated skin lesions may appear, known as secondary annular erythema.

1. Livre-docente - Professor associado da Faculdade de Medicina da Universidade de São Paulo – USP, São Paulo, SP
2. Bacharel em Biomedicina; doutoranda em Ciências Médicas - Pós-graduada da Faculdade de Medicina da Universidade de São Paulo – USP, São Paulo, SP
3. Mestre em Fisiopatologia Experimental; doutora em Ciências Médicas - Biologista do LIM17 – Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo – HCFMUSP, São Paulo, SP
4. Médica; doutoranda em Ciências Médicas - Pós-graduada da Faculdade de Medicina da Universidade de São Paulo – USP, São Paulo, SP
5. Médica; doutora em Reumatologia - Médica assistente do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo – FMUSP, São Paulo, SP
The secondary stage appears days or months after the initial contagion and is characterized by articular, neurological, and cardiac complications.

Post-LD syndrome or TAPOS (Tick Associated Poly-Organic Syndrome) is a clinical entity observed in the USA, very controversial and undefined, emerging in LD patients after antibiotics treatment. It is characterized by the development of persistent symptoms, with duration of more than 6 months, with myalgia, arthralgia, radicular pain, dysesthesias, neurocognitive symptoms and intense fatigue.6

LD diagnostic confirmation in Northern Hemisphere is basically serological, since the culture is a slow and improductive procedure, and the PCR is rarely employed, because it identifies only cases in which borrelias are circulating or deposited in tissues.

The treatment for LD is based upon the use of antibiotics. In the Northern Hemisphere the persistence of spirochetes in the host after adequate use of antibiotics is not accepted. Therefore, the hypothesis of clinical recurrence and new treatment with antibiotics is not admitted, except in case of articular relapses which are interpreted as manifestations of autoimmunity. In this sense, the denomination of chronic LD is used to designate clinical cases that were not recognized at early stage and not efficiently treated with antibiotics.

History of LD research in Brazil

LD research in Brazil started in 1989.9 After intense disclosure of the theme to the Brazilian medical class, the first case of the disease were identified in 1992.10

As new patients were being discovered, epidemiological, clinical and laboratorial differences between LD described in the Northern Hemisphere and the Brazilian type were observed.11-14 From the epidemiological point of view, differently from the United States of America (USA) and Eurasia, ticks belonging to Ixodes ricinus complex were not identified at risk areas for this zoonosis. Clinically, despite the occurrence of classical ME and habitual systemic complications in LD, the Brazilian disease had a recurrent course, especially if the treatment with antibiotics was introduced after three months from the beginning of the infection. In laboratorial terms, bacteria from the B. burgdorferi sensu lato complex were not isolated in biological fluids and tissues whatsoever. The antibodies against B. burgdorferi of North American or European origin, although relevant for diagnosis, reveals low and oscillating titres, rapidly disappearing in the blood or cephalorachidian liquid. Brazilian patients also display high frequency of antibodies directed against self cellular constituents.

Thus, the disease identified in the country received numerous denominations such as LD-like disease, Infectious-Reactive Lyme-like syndrome (SIRLS)15 or Brazilian Lyme Disease-like syndrome aiming at differentiating it from classical LD.

Researches conducted at the Laboratory of Investigations in Rheumatology of the Hospital das Clínicas, School of Medicine, Universidade de São Paulo (LIM-17 HCFMUSP) show an occurrence of microorganisms with morphologic structures similar to Mycoplasma spp, Chlamydia spp, and spirochetes without flagella in the peripheral blood of patients with SIRLS, when visualized with Electronic Microscopy (EM).15

However, once the frequency of positive serologic tests for the microorganisms mentioned was similar in the individuals with SIRLS and in the control group, and the molecular tests were negative for Mycoplasma spp and Chlamydia spp (Yoshinari NH, Mantovani E - Reports FAPESP processes nº 05/56166-8 and 06/54837-5 - unpublished data), it was suggested, based on information from medical literature that these different structures with atypical morphology could represent morphologic variations of latent spirochetes.16,17

Supposing that the SIRLS etiologic agent is a Borrelia of atypical morphology, the discovery deserves a special significance, because in medical literature, diseases caused by spirochetes with this morphological presentation have never been described. Generally, L-form bacteria are considered non-pathogenic and, from the morphologic point of view, they are identical to Mycoplasmas,18,19 which are bacteria deprived of cellular wall.

It is known that spirochetes can also undergo other structural transformations, assuming the shape of cysts or dense bodies, when bacteria are submitted to unfavorable cultivation conditions, as in changes in nutrients, pH, and presence of antibiotics. A return of these latent structures to habitual spiral morphology occurs when cultivation conditions improve.16,17 In Brazil, the isolation of spirochetes in spiral shape was never possible in biologic materials originated from SIRLS patients, even using cultivation media proper to this microorganism.

Thus, based on the LIM-17 HCFMUSP researches, emerged the concept of a new zoonosis, imitating LD, typically Brazilian, caused by spirochetes, possibly borrelias, which permanently preserve the atypical form, both in vertebrate and invertebrate hosts. This concept of infection caused by spirochetes in the latent morphology can justify the numerous particularities observed in SIRLS, such as difficulty of cultivation of the etiologic agent in the BSK modified medium; absence of spirochetes in the typical helicoidal spiral presentation; low immunologic response against B. burgdorferi in SIRLS patients; frequent clinical recurrences and the emergence of immune-allergic disturbances.

Brazilian physicians should be informed about the non-existence in the country of conclusive reports of classical LD with typical clinical and laboratorial characteristics found in the Northern Hemisphere. On the other hand, they should be alert to the existence of a severe and highly morbid zoonosis transmitted by ticks. It has an infectious initial character; when not recognized and treated early, it develops recurrent systemic complications throughout its evolution, determining the emergence of chronic diseases, especially with neurological and articular symptoms, followed by manifestations of autoimmunity.

In order to dissociate this Brazilian zoonosis from the LD, aiming at encouraging research and diffusion of knowledge on this emerging disease to the Brazilian medical class, the nomenclature has been changed to Baggio-Yoshinari Syndrome (BYS).20

Baggio-Yoshinari Syndrome

Definition

It is a disease of infectious origin, transmitted by ticks of the genera Amblyomma and/or Rhipicephalus, caused by uncultivable spirochetes of the B. burgdorferi sensu lato complex at atypical morphology (Yoshinari NH, Mantovani E - Relatórios FAPESP processes nº 05/56166-8 e 06/54837-5 - unpublished data).
data), which determines systemic and relapsing complications, including immunologic disorders, throughout the prolonged clinical evolution.

**Etiology**

The Baggio-Yoshinari Syndrome (BYS) is caused by spirochetes with atypical morphology and latent behavior, not spiraled, similar to *Mycoplasma* spp, *Chlamydia* spp and bacteroids. They are uncultivable in aerobic and anaerobic settings, including the BSK medium proper to the growth of borrelias. They present a slow and momentary growth in a medium known as SP4 (Figure 1), ideal for the development of Mollicutes belonging to genus *Spiroplasma*, bacteria possessing little movement, without cell wall, and cellular membrane rich in cholesterol. Furthermore, bacteria-like spirochetes have the ability to invade *in vitro* culture of endothelial cells (Figure 2).

In analyzing SYB patient’s peripheral blood in dark field microscopy, around 90% display movable structures similar to spirochetes. However, these microorganisms are present also in around 20% of normal individuals. These structures, when analyzed in electron microscopy, display formations that resemble long bacteroids without flagella, cysts and dense bodies, which would be, in fact, morphological variations of pathogenic spirochetes adapted to survive in vertebrate and invertebrate hosts.

Structurally modified spirochetes, due to deletion or genic repression, express less lipoproteins of external membrane and periplasmic flagella, becoming resistant to the action of antibodies and antibiotics, besides provoking a lower immunological response on the part of the host. At invading cells such as the endothelial ones, these latent spirochetes defend themselves better from external aggression and are capable of causing recurrent clinical symptoms.

Structures visualized in the EM analysis in normal individuals resemble Mycoplasms and possibly translate the blood circulation of saprophyte bacteria of different species in the L-form presentation (cell wall deficient bacteria), generally non-pathogenic.

Molecular Biology tests such as PCR have failed in identifying *B. burgdorferi*, in using *primers* identifiers of DNA targeting flagella and lipoproteins of external membrane (Osp). At the moment, researches in the LIM-17 HCFMUSP attempt to discover other generic markers, such as *primers* targeting conserved genes responsible for spirochete infection and survival at different hosts.

**Vectors**

Field researches conducted at geographic risk regions where there have been cases of BYS showed the occurrence of ticks belonging to the species *Amblyomma cajennense* and *Ixodes loricatus*. It is believed that the tick transmitting spirochetes to men is *A. cajennense*, because besides biting men, the development of BYS has already been observed after the accidental biting by this species of tick.

Ticks from the *Rhipicephalus microplus* species cannot be discarded as participant of zoonosis transmission cycle, because there is a coexistence of antibodies for *B. burgdorferi* and *Babesia bovis* in BYS patients, and this tick species is the responsible agent for the transmission of babesiosis in bovines. Other arthropods as flies, mosquitoes and louses might also be involved in the BYS epidemiological cycle.

It is important to highlight that in geographical risk areas for BYS, ticks from the *Ixodes ricinus* complex were not found. It is well known, that this vector is responsible for the transmission of classical LD in the USA and Eurasia.

The Brazilian biodiversity in reservoir animals and ticks, as well as climactic differences, would be the factors implied in the emergence of latent spirochetes, possibly borrelias, in cystic presentation, very different from spiraled microorganisms found in the Northern Hemisphere.
Reservoirs and hosts

Field researches in areas of BYS occurrence showed the presence of wild rodents and marsupials, potential reservoir animals in Brazil often contaminated with spirochete-like microorganisms, which equally do not grow in habitual cultures settings and are not identified by the PCR tests. Particularly in the State of Espírito Santo, there is an important association between the occurrence of BYS cases and the presence of capybaras, suggesting that ticks parasitizing these rodents may participate in the BYS’s epidemiological cycle. Of equal importance is the development of BYS’s clinical symptoms after the contact with domestic animals such as horses, dogs, and bovines.

Clinical picture

In Brazil, patients are diagnosed in their early or latent stage (reoccurrence). In the acute phase, randomly defined as disease with less than 3 months of evolution after the biting by ticks, it is perceived that around 50% develop macular or papular lesion, centrifugal growth, reddish border and clearer center, in the bitten place, called migratory erythema (ME). In other cases, the lesion is homogeneously reddish and, in yet other situations, it appears by the coalescence of multiple and minuscule punctiform lesions.

The period of incubation between the biting and the lesion appearance is around 10 days, but it may vary from 3 days to weeks. The skin lesion usually lasts for around 30 days, with the ME persisting for several months in some cases. In the phase of dissemination of microorganisms, fever and other flulike symptoms emerge. In this stage, new skin lesions may appear, multiple and less expansive than the initial one, called secondary annular.

When usual treatment with antibiotics is not initiated until days or months after the initial contagion, secondary complications such as cutaneous, neurological, articular and cardiac relapses may develop. In Brazil, articular and neurological complications occur in around 35% of the cases and cardiac, in 5%. Arthritis happens generally in big joints, especially knees, with oligoarthritis pattern. The inflammatory outbreak usually lasts for weeks to months, the synovia biopsy reveals unspecific inflammation and the synovial fluid displays an elevated number of leukocytes. Initial arthritis outbreaks tend to regress spontaneously, but in the stages of relapse there is the tendency to the development of polyarthritis of continuous character, with no improvement periods, resembling articular manifestations of rheumatoid arthritis.

The BYS neurological picture, similarly as LD, is characterized by the triad of lymphomonocitary meningitis, cranial neuritis, and peripheral radiculopathy, and less commonly cases of encephalitis and/or encephalomyelitis. The typical manifestations of cardiac involvement are arrhythmias, which may last for months and usually does not need the implantation of artificial pacemaker.

The distinctive clinical aspect of BYS is the high frequency of relapses, especially when the patients are not diagnosed and treated early in the acute phase. It is important to highlight that episodes of recurrences are generally not diagnosed by the physicians, because epidemiological data occurred in the past are not inquired or associated with current symptoms. Besides that, cutaneous manifestations and flulike symptoms tend to disappear throughout the prolonged clinical evolution, making the prolonged BYS diagnosis even more difficult. Despite the difficulties, the physician in face of a patient with the suspicion of BYS in latent phase must be attentive and question on events that happened years or decades before, such as: previous history of being bitten by ticks, residence in proximity with woods in contact with domestic or wild animals, previous episodes of fever of unknown etiology, skin lesions like ME or secondary annular lesion, arthritis, meningitis, cranial or peripheral neuropathies, uveitis, psychiatric disturbances etc.

The main clinical manifestations observed in BYS are described below:

1. Cutaneous: migratory erythema (Figure 3); secondary annular erythema, benign lymphocytoma, atrophic chronic acrodermatitis, paniculitis and skin lesions similar to scleroderma at the initial tick bite place.

2. Osteomuscular: arthritis, arthralgia, myositis, Chronic Fatigue Syndrome (CFS). This syndrome is defined as physical or mental distress with duration over six months, not improving with rest and exacerbated by physical activities. CFS is defined in the presence of four of the following symptoms: prolonged fatigue, headache, myalgia, memory or concentration loss, arthralgia, throat ache, cervical adeno-megaly and sleep disorder.

3. Neurological: lymphomonocitary meningitis; cranial nerves neuritis (facial paralysis, diplopia, deafness, dysphagia, dyslalia, trigeminal nerve neuralgia); sensitive-motor peripheral radiculopathies; Guillain-Barré syndrome; multiplex mononeuritis, seizures, encephalomyelitis, encephalopathy, sphincter dysfunction.

4. Cardiac disorders such as arrhythmias and heart failure due to cardiomegaly.

5. Psychiatric disorders as severe depression, suicide attempts, panic syndrome, bipolar disorder, schizophrenia.

6. Social adequacy disorders as running away from school, isolation, leaving jobs.
7 - Intrinsic ocular disorders as uveitis, chorioretinitis and retinal arteritis. 
8 - Cognitive disorders including memory shortage, difficulty of expression, sleep disorders, difficulty of concentration, memorizing and reasoning. 
9 - Immune-allergic dysfunctions with higher sensitivity to drugs and foods, urticariases and severe symptoms as acquired angio-neurotic edema. 

**Diagnosis** 
BYS diagnosis is essentially clinical and the HCFMUSP LIM-17 suggests a diagnostic guide based on the presence of major and minor parameters (Table 1) 

Laboratorial data must be carefully interpreted in Brazil. Exams indicating acute inflammatory activity such as hemosedimentation speed, C reactive protein and mucoproteins might be negative, even under inflammatory processes, such as arthritis, meningitis or neuritis. This clinical-laboratorial dissociation is a common aspect of the BYS and it indirectly shows how much the latent microorganisms are adapted to survive in the host. Laboratorial findings like anemia, leucopenia, transaminases elevation or bilirubins in BYS patients may suggest coinfections with other tick borne zoonoses, such as babesiosis and ehrlichiosis. Patients who develop torpor, mental confusion or coma, associated with cutaneous exanthem, may be useful when there is the suspect of neurological involvement at HCFMUSP the quantity of bands present is valued instead of the one standardized in Northern hemisphere, because in the LIM-17 HCFMUSP the quantity of bands present is valued instead of the occurrence of specific bands, as in other continents. The research of anti-B. burgdorferi antibodies in cephalorachidian liquid (ELISA) may be useful when there is the suspect of neurological involvement at BYS, but it bears the same restrictions as those of serological study. In general, normal healthy individuals do not present anti-Borrelia antibodies in the CRL, but in the ELISA test, it might be positive in many infectious or autoimmune conditions. 

BYS patients develop autoantibodies throughout the prolonged clinical evolution. Data yet unpublished indicate that around 50% of BYS patients present autoantibodies against human neurons' membrane extract, confirming previous studies that had already revealed the existence of antibodies against rabbits' caudate nucleus protein in BYS patients. Other immunologic disorders were also described in Brazil, such as antinuclear antibody (ANA), anticardiolipin, hypergammaglobulinemia and IgE elevation. 

Current researches in progress at LIM-17 HCFMUSP are directed towards Molecular Biology tests, in an attempt to demonstrate that the BYS etiological agent, despite the appearance at its cystic form, would still be a spirochete belonging to the genus Borrelia. 

**Treatment** 
The treatment is dependent on the BYS staging, an aspect not always easy to be defined, except when in face of a patient with acute disease, who has developed ME after being bitten by a tick and has recently visited a risk area. Generally, the patients look for the physicians under late complications and in these conditions, as was previously highlighted, the diagnosis is extremely complex and difficult. 

Primary BYS infection is treated with doxycycline 100 mg twice a day for the minimum period of 30 days. Children may receive amoxilin or azithromycin for the same period. Recurrent early outbreaks may be treated with the same antibiotics by prolonged period of three months, but the results can be inconstant. 

In the presence of neurological complications as meningitis, encephalitis, neuritis, or under recurrent arthritis, is recommended a therapeutic schedule with ceftriaxone 2g/IV/day given during serological tests (ELISA and Western-blotting) is employed. Among diseases that cause false-positive serology are reported syphilis; visceral leishmaniasis; autoimmune diseases such as systemic lupus erythematosus, scleroderma and rheumatoid arthritis; viral infections, acute rickettsioses; chronic neuropathies. Patients with BYS develop positive serology (ELISA or WB) to B. burgdorferi in approximately 65% of cases, while in normal individuals the frequency of positivity is nearly 16%. In the acute stage of the zoonosis there is the dominance of IgM class antibodies, and in the convalescence period, that of IgG, but this distinction tends to disappear in relapsing outbreaks. Small oscillations of titles or results do not indicate that there have been modifications in clinical evolution. It is worth highlighting that the interpretation of serological results performed with methodologies adapted to our setting is different from those performed in the USA and Eurasia. 

Immunoenzymatic test (ELISA) is done with total sonicated antigen of B. burgdorferi strain G39/40 of North-American origin, following the same methodology adopted in the USA. On the other hand, the interpretation of Western-Blootting is quite different from the one standardized in Northern hemisphere, because in the LIM-17 HCFMUSP the quantity of bands present is valued instead of the occurrence of specific bands, as in other continents. The research of anti-B. burgdorferi antibodies in cephalorachidian liquid (ELISA) may be useful when there is the suspect of neurological involvement at BYS, but it bears the same restrictions as those of serological study. 

In general, normal healthy individuals do not present anti-Borrelia antibodies in the CRL, but in the ELISA test, it might be positive in many infectious or autoimmune conditions. 

BYS patients develop autoantibodies throughout the prolonged clinical evolution. Data yet unpublished indicate that around 50% of BYS patients present autoantibodies against human neurons' membrane extract, confirming previous studies that had already revealed the existence of antibodies against rabbits' caudate nucleus protein in BYS patients. Other immunologic disorders were also described in Brazil, such as antinuclear antibody (ANA), anticardiolipin, hypergammaglobulinemia and IgE elevation. 

Current researches in progress at LIM-17 HCFMUSP are directed towards Molecular Biology tests, in an attempt to demonstrate that the BYS etiological agent, despite the appearance at its cystic form, would still be a spirochete belonging to the genus Borrelia. 

**Table 1 - Diagnostic criterion for BYS adopted by the Discipline of Rheumatology at Hospital das Clínicas da Faculdade de Medicina da USP. It is considered positive when the patient presents three of the major parameters or two major and two minor parameters**

**MAJOR PARAMETERS**

- Compatible epidemiology at the beginning of the infection: tick bite, visit to risk areas, visualization of ticks in the environment or animals, presence of sick animals at the place.
- Positive serology for Borrelia burgdorferi (ELISA or WB) as standardized at HCFMUSP LIM-17.
- Pertinent clinical symptoms: ME or systemic complication (articular, neurological, cardiac or ocular).

**MINOR PARAMETERS**

- Recurrence episodes
- Visualization of spirochete-like microorganisms at dark field microscopy.
- Chronic fatigue syndrome.

BRAZILIAN LYME-LIKE DISEASE OR BAGGIO-YOSHINARI SYNDROME: EXOTIC AND EMERGING BRAZILIAN TICK-BORNE ZOONOSIS.
30 days, followed by two additional months of doxycycline 100 mg twice a day. In this latent disease stage it is usual to asso-
icate hydroxychloroquine in the dosage of 400 mg/day during a
prolonged period of time. Symptoms such as chronic fatigue and
cognition disorders have a poor response to the use of antibiotics
and usually deserve other forms of therapeutic approach.15,24

There is no consensus on the treatment of relapsing symp-
toms of BYS at prolonged clinical follow up. There are cases of
good response to antibiotics, as well as those that are non-
responsible. In the Discipline of Rheumatology of HCFMUSP, the
patients with articular involvement, mainly at polyarticular and
recurrent stage, receive the same drugs adopted to treat patients
with rheumatoid arthritis, that is, they receive anti-inflammatory
drugs and disease-modifying anti-rheumatic drugs (DMARDs).

New researches are conducted to understand the role of
autoantibodies in the BYS pathogenesis. There is a quest for soro-
logical markers which allow the distinction of BYS neuropathy
or chronic arthritis from the other affections considered specific,
such as multiple sclerosis, rheumatoid arthritis or spondyloar-
thopathies. Currently, it is very difficult for physicians, to know
when to stop giving antibiotics and search for new therapeutic options for BYS patients with prolonged disease.

**Conclusions**

Summing up, there is an original and exotic Brazilian tick
borne disease named Baggio-Yoshinari syndrome, which is very
different from classical LD. In spite of many diagnostic difficul-
ties, Brazilian physicians must be prepared to identify this new
emerging zoonosis, since its frequency is growing fast in the
country. The diagnosis and treatment at early disease stage are
very important, because antibiotic treatment is efficient and can
cure the illness. On the contrary, at latent stage, treatment is less
effective, perhaps due to development of autoantibodies directed
to self antigens. It is interesting to highlight that, even in the
Northern Hemisphere, there are many unanswered questions
related to LD understanding, such as doubts concerning infec-
tion persistence, dissociation between symptoms and laboratory
findings and treatment of chronic LD.

**Financial support:** Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) and Ministério da Saúde

**No conflicts of interest:** declared concerning the publication of this article

**References**

30. Mendel H, Steere AC, Reinhardt BN, Yoshinari NH, Munisat TL. Lack of antibo-

Aceito para publicação: 30/09/09
Aceito para publicação: 11/03/10