

# Neurological manifestations in Baggio-Yoshinari Syndrome (Brazilian Lyme disease-like syndrome)

Samuel Katsuyuki Shinjo<sup>1</sup>, Giancarla Gauditano<sup>1</sup>, Paulo Euripedes Marchiori<sup>2</sup>,  
Virgínia Lúcia Nazário Bonoldi<sup>3</sup>, Izaias Pereira da Costa<sup>4</sup>, Elenice Mantovani<sup>5</sup>, Natalino Hajime Yoshinari<sup>6</sup>

## ABSTRACT

**Introduction:** Lyme disease (LD) is a tick-borne disease, caused by *Borrelia burgdorferi sensu lato* spirochetes, transmitted by *Ixodes ricinus* complex ticks, which leads to multiple systemic clinical manifestations. In Brazil, a different syndrome is described that mimics LD symptoms, but that also manifests high frequencies of recurrent episodes and immune-allergic manifestations. It is transmitted by the *Amblyomma cajennense* tick and the etiological agent is an uncultivable spirochete with atypical morphology. Due to its particularities, this emerging zoonosis has been called Brazilian LD-like syndrome or Baggio-Yoshinari Syndrome (BYS). **Objective:** To describe the neurological spectrum of BYS. **Patients:** Thirty patients with neurological symptoms of BYS were analyzed. **Results:** Mean age of patients was 34.2 ± 13.3 years old (6 to 63 years); 20 were females and 10 males. A high number of recurrent episodes (73.6%) and severe psychiatric or psycho-social disturbances (20%) were distinguishing features. Erythema migrans similar to those seen in the Northern hemisphere was identified in 43.3% of patients at disease onset. The recurrence of skin lesions diminished as the disease progressed. Articular symptoms (arthritis) happened in nearly half of patients at BYS onset and during relapsing episodes. **Conclusions:** The BYS is considered a new tick borne disease in Brazil that differs from classical LD observed in the Northern hemisphere. BYS replicates most of the neurological symptoms observed in LD, except for the additional presence of relapsing episodes and the tendency to cause chronic neurological and articular manifestations.

**Keywords:** lyme disease, tick borne disease, spirochete, neuroborreliosis, lyme disease-like syndrome.

## INTRODUCTION

Lyme disease (LD) is a tick-borne disease caused by *Borrelia burgdorferi sensu lato* spirochete and transmitted by *Ixodes ricinus* complex ticks. It causes multiple systemic clinical manifestations which may be articular, cardiac, neurological and cutaneous. The typical skin lesion is called erythema migrans (EM)<sup>1-3</sup>.

Since the early 1990s, many manuscripts on LD have been published in Brazil<sup>4-21</sup>, showing that the medical condition exhibited by Brazilian patients, closely resembled that seen in the Northern hemisphere, including the appearance of EM lesions<sup>10</sup> and all the systemic symptoms of LD<sup>6,11</sup>. However, our previous research has demonstrated significant differences: 1- The etiological agent not able to be cultivated; 2- Spirochete-like structures were observed in the peripheral blood of

patients; 3- Electron microscopy analysis of these structures disclosed microorganisms resembling atypical spirochetes (L-form bacteria); 4- Atypical spirochetes invaded culture of endothelial cells *in vitro*; 5- Polymerase chain reaction (PCR) assays were always negative, also when conservative primers for genus *Borrelia* were employed; 6- Humoral and cellular immunity against *B. burgdorferi* G 39/40 of American origin revealed low reactivity; 7- Absence of human blood sucker *Ixodes ricinus* complex ticks at risk areas; 8- High incidence of recurrent episodes when patients were not treated immediately at disease onset (within three months); 9- High frequencies of auto-antibodies such as those against anti neuronal components; 10- Tendency to develop allergic symptoms induced by drugs or foods, and also extraordinary and severe cases of angioedema.

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1. Assistant Physicians, Dermatology Department, Hospital das Clínicas of the Medical School of Universidade de São Paulo (HC/FMUSP), São Paulo, Brazil

2. Professor, Neurology Department FMUSP, São Paulo, Brazil

3. Professor, Pharmacist, Rheumatology Department, FMUSP, São Paulo, Brazil

4. Physician, Rheumatology Department, Universidade Federal de Mato Grosso do Sul, Mato Grosso do Sul, Brazil

5. PhD Student, Biomedicine, Rheumatology Department, FMUSP, São Paulo, Brazil

6. Professor, Rheumatology Department, FMUSP, São Paulo, Brazil

Correspondence to: Natalino Hajime Yoshinari. Av. Dr. Arnaldo, 455, 3º andar, sala 3139, CEP: 01246-903, São Paulo, SP, Brasil. Fax: (11) 3061-7490. Tel: (11) 3061-7492. E-mail: yoshinari@lim17.fm.usp.br

For these reasons, the name Baggio-Yoshinari Syndrome (BYS)<sup>10</sup> was proposed to substitute all the previous nomenclatures given to Brazilian LD like illness or syndromes (BLDLS). Furthermore, due to many particularities, this disease was considered an original tick borne disease, indicating that inappropriate comparisons with LD should be avoided. In this sense, low serological immune response to *B. burgdorferi sensu lato* or repeated negative PCR assays observed in BYS patients could represent laboratorial hallmarks of BLDLS, despite of mistakes due to technical flaws.

BYS has now been defined as a vector-borne disease caused by atypical morphological spirochetes at vegetative presentation and transmitted by arthropods not belonging to the *I. ricinus* complex, which replicates all the clinical symptoms described in classical LD, with the addition of a high frequency of relapse episodes and autoimmune manifestations<sup>10</sup>. Likely transmission vectors of BYS belong to the *Amblyomma* and *Boophylus* genus, and this important difference could explain all the particularities observed in BYS versus LD.

Same features of BYS also resemble the Southern tick-associated rash illness (STARI) or Masters disease, which is found in the Southern USA<sup>22-24</sup>. This vector belongs to the genus *Amblyomma*, where the etiological agent *B. lonestari* is uncultivable in BSK medium, and the disease develops only EM-like skin rash without systemic symptoms, but treatment with doxycycline is considered prudent<sup>23</sup>. As outlined previously, BYS differs greatly to STARI, because the Brazilian zoonosis causes clinical manifestations similar to classical LD.

The neurological manifestations of BLDLS were first described by Yoshinari *et al.*<sup>12</sup> including patients with peripheral neuritis, meningitis and cranial neuritis (facial nerve palsy, diplopia and deafness). Since then, other neurological affections have been described in BLDLS such as typical meningitis<sup>16</sup>, bilateral facial and cochleovestibular palsy<sup>17</sup>, bilateral papilledema and corneal keratitis<sup>20</sup>.

The aim of this manuscript was to describe the neurological features of BYS based on the evaluation of 30 consecutive patients with this organic manifestation. Furthermore, some patients were followed up for a prolonged period to study symptoms related to relapse episodes.

## PATIENTS AND METHODS

**Patients.** Only patients examined by neurologists or psychiatrists practicing at different Brazilian Medical Schools were included. Nineteen patients were referred by the Hospital das Clínicas da Faculdade de Medicina da Universidade de

São Paulo (HC/FMUSP), while others were drawn from other Institutions, the majority located within São Paulo State.

The diagnostic criteria for BYS<sup>10</sup> comprise three major and three minor parameters. The major parameters are: 1- Positive epidemiological data at disease onset; 2- Positive serology for *B. burgdorferi* G 39/40 of North American origin (ELISA or WB) and 3- Presence of EM or any systemic manifestation (arthritis, neurological, cardiac or ocular). The minor parameters are: 1- Chronic fatigue symptoms for at least six months; 2- Presence of “spirochete-like” structures in peripheral blood observed on dark field microscopy and 3- Recurrent episodes of cutaneous or systemic symptoms. BYS is considered positive in the presence of three major parameters or two major plus two minor parameters. Intrinsic eye lesions such as retinal arteritis, uveitis or optic neuritis are considered important parameters of BYS due to their frequency and severity. The serologic assays to identify antibodies against *B. burgdorferi* were modified at our laboratory to improve test sensitivity. Thus, the laboratorial procedures and interpretation of WB differ significantly to those adopted in the Northern Hemisphere. The antigen of North American origin was kindly provided by Dr Allen C. Steere.

All of the patients exhibited neurological symptoms of classical LD and fulfilled Brazilian criteria for BYS. The patients signed an informed consent and the protocol had been previously approved by the Hospital Ethics Committee (n° 776/06).

Serology against *B. burgdorferi* in sera of BYS patients.

1) Enzyme-linked immunosorbent assay (ELISA). The assay was performed by standard methods with some modifications<sup>25-27</sup>. Briefly, the microtitration plates (EIA/RIA plate, Costar) were coated with 200  $\mu$ L of a 0.015 mg/mL solution of the whole sonicated *B. burgdorferi* G39/40 strain diluted in 0.05 M sodium carbonate pH 9.6, and incubated overnight at 4 °C. The plates were then washed three times with phosphate buffer solution (PBS) containing 0.05% Tween 20 and blocked with PBS Tween 20 and 5% skimmed milk, pH 7.4. The washing procedure was repeated and test samples and control sera were diluted in blocking solution and plated in duplicate (200  $\mu$ L/well). The samples, along with 8 negative control sera, were diluted at 1/400 for IgG and 1/100 for IgM antibodies, and the positive control sera (provided by Dr. Allen C. Steere) were diluted using serial two ratio dilutions starting at 1/400 (IgG) or 1/100 (IgM). After incubation at room temperature for one hour, the washing procedure was repeated, and the goat alkaline phosphatase-conjugated anti-human IgG and IgM (Sigma Chemical Co.) diluted 1/1,000 in blocking solution added. After incubation and washing procedures, the substrate p-nitrophenyl sodium phosphate (Sigma Chemical Co.) diluted at 1 mg/mL in glycine buffer pH 10.5 was added.

The plates were read at 405 nm on a Titertek Multiscan MCC/340 (Flow Laboratories), and the reaction stopped when the first dilution of the positive control serum reached the optical density value near 1.0. Cut-off value was obtained by considering the mean optical density plus three standard deviations of the 8 negative control sera. Optical densities (OD) higher than cut-off values were considered positive and the titers were estimated by regression curve.

2) Western blot (WB)<sup>25,26</sup>. Electrophoresis and immunoblotting were performed as previously elsewhere, with some modifications. Briefly, 750 mg of whole sonicated spirochete proteins (G39/40 strain), reduced with SDS was submitted to electrophoresis (Mini-Protean II System, Bio Rad) in 10% acrylamide gel. After running the procedures, gel proteins were transferred to nitrocellulose paper overnight (Mini Trans Blot System, Bio Rad), and the paper cut into strips, and then washed in distilled water. One strip containing *B. burgdorferi* antigens and another with molecular weight markers were separated and stained with a solution-diluted 1:1 of colloidal gold (Bio Rad). The other strips were blocked with TBS 0.1% Tween 20 and 5% skimmed milk solution for 1 hour at room temperature and then washed five times with TBS 0.1% Tween 20. The sera samples to be tested (positive serum, negative controls and test sera) were diluted at 1/100 in blocking solution and placed to incubate together with strips for 1 hour at room temperature. After washing, the strips were incubated for 1 hour with goat alkaline phosphatase-conjugated anti human IgG and IgM (Sigma Chemical Co.) diluted at 1/1,000 with blocking solution. Washing was repeated and substrate consisting of NBT/BCIP diluted in bicarbonate buffer pH 9.8 was added. The reaction was blocked when positive control developed color.

The assay was considered positive when test sera samples exhibited presence of four or more IgG bands or two or more IgM bands, or at least two IgG and one IgM bands. This standardization was adopted because the pattern of Western blot reactivity is different in Brazil compared to those observed in North Hemisphere, possibly due to presence of atypical spirochetes in Brazil.

## RESULTS

The demographic and clinical features of 30 BYS patients with neurological manifestations are described in Table 1. Of these patients, 24 (80%) reported relevant epidemiological data at disease onset period. Sixteen patients (53.3%) reported tick bite history, 17 subjects (56.7%) had visited high-risk areas and 6 individuals (20%) reported direct contact with domestic animals.

Sixteen patients (53.3%) were included in the group of early BYS stage (disease onset within three months of first consultation), in whom neurological symptoms had started between three and 45 days. Fourteen patients were classified as belonging to late BYS, and whose neurological symptoms had begun between three months and four years of disease onset, with a mean period of 20.6 months.

The neurological symptoms observed in BYS patients are shown in Table 2. Meningeal irritation symptoms were mild, often accompanied by minimal cervical pain, fever, nausea, and vomiting complaints. Peripheral radiculitis occurred in 24 (73.3%) patients. Ocular complaints were very frequent (36.7%) and in most cases were associated with impairment of cranial nerve or with peripheral radiculopathy. The main eye manifestations were eye-lid ptosis, anisocoria, strabismus, mydriasis, papilledema, diplopia, ophthalmoparesis, photophobia, corneal reflex disturbance, and Claude Bernard syndrome.

Another important finding was the high frequency of psychiatric or psycho-social disturbances, and the patients had not previous history of psychiatric illness. One patient had severe depression, characterized by a suicide attempt, loss of appetite, and social indifference. Another individual developed unusual aggressive behavior. Cognitive disturbances manifesting with non-specific symptoms including memory loss, sleep disturbance, impairment of word retrieval, mood impairment were diagnosed in eight patients.

Clinical manifestations were classified into neurological syndromes and meningitis was found in half of the patients (50%), peripheral radiculitis in 16 (53.3%) and cranial neuritis in 13 cases (43.3%). The facial and oculomotor cranial nerves were the most involved, identified in 7 (23.3%) and 6 patients (20%), respectively. In general, there was co-existence of multiple neurological symptoms, especially with those reported in the classical triad manifestations of neuroborreliosis, including meningitis, cranial neuritis and peripheral radiculitis.

Encephalomyelitis, characterized by unifocal or multifocal inflammatory processes of the central nervous system and/or spinal cord, was defined as progressive slow involvement of white matter, and were present in 10 patients (33.3%), half of them at an early-disseminated stage. Encephalomyelitis was clinically characterized by presence of spastic paraparesis, transverse myelitis, cerebellar syndromes, hemiparesis or movement disorders. In this group of encephalomyelitis, three cases had cerebellar ataxia, two presented transverse myelitis complicated by anal or bladder sphincter dysfunctions, 6 patients developed psychiatric manifestations of organic etiology and one presented seizures.

Twelve patients from the early BYS group received antibiotic treatment after diagnosis and all cases had a good therapeutic response, confirmed by partial or total resolution of symptoms. The same antibiotic schedule used for classical LD was employed in BYS cases. This treatment was based on the use of ceftriaxone 2 g/day or penicillin 2.4 million units/day for 15 to 30 days. Due to the high frequency of recurrence in BYS, an additional course of doxycycline 100 mg twice a day was administered for one or more months. Four patients in

**Table 1**  
Demographic and clinical features of Baggio-Yoshinari syndrome with neurological manifestations

Cases, n (%)	30 (100)
Sex, female (%)	20 (66.7)
Mean age ± standard deviation (year)	34.2 ± 13.3 (6 to 63 years)
Precedence (State)	
São Paulo (%)	25 (83.3)
Rio de Janeiro (%)	2 (6.7)
Minas Gerais (%)	1 (3.3)
Mato Grosso do Sul (%)	1 (3.3)
Rio Grande do Sul (%)	1 (3.3)
Epidemiological data on tick history (%)	24 (80.1)
Constitutional symptoms (%)	30 (100)
Erythema migrans (%)	13 (43.3)
Articulation manifestation (%)	17 (56.7)
Muscle manifestation (%)	3 (10.0)
Neurological manifestation	
Early (%)	16 (53.3)
Late (%)	14 (46.7)

**Table 2**  
Neurological manifestations observed in 30 patients with Baggio-Yoshinari syndrome

Symptoms	Frequency (n=30)	Early BYS (n=16)	Late BYS (n=14)
Meningismus	15 (50.0%)	9 (56.3%)	6 (42.9%)
Peripheral motor radiculitis	12 (40.0%)	9 (56.3%)	3 (21.4%)
Peripheral sensitive radiculitis	10 (33.3%)	7 (43.8%)	3 (21.4%)
Ocular symptoms	11 (36.7%)	7 (43.8%)	4 (28.5%)
Peripheral facial nerve palsy	8 (26.7%)	5 (31.3%)	4 (28.5%)
Hearing disturbance	3 (10.0%)	2 (12.5%)	1 (7.1%)
Dysphagia	2 (6.7%)	1 (6.3%)	1 (7.1%)
Dysarthria	2 (6.7%)	0 (0.0%)	2 (14.3%)
Loss of balance	1 (3.3%)	0 (0.0%)	1 (7.1%)
Psychiatric disorders	6 (20.0%)	2 (12.5%)	4 (28.5%)
Cognitive disturbance	8 (26.7%)	4 (25.0%)	4 (28.5%)
Muscle fasciculation	1 (3.3%)	0 (0.0%)	1 (7.1%)
Seizures	2 (6.7%)	0 (0.0%)	2 (14.3%)
Coma	1 (3.3%)	0 (0.0%)	1 (7.1%)
Ataxic gait	3 (10.0%)	3 (18.8%)	0 (0.0%)
Sphincter control loss	2 (6.7%)	1 (6.3%)	1 (7.1%)

BYS: Baggio-Yoshinari syndrome

the early-disseminated group received no antibiotic treatment, and two of these presented disease relapse episodes during follow up.

Out of 14 patients from the late BYS group, 11 were treated with antibiotics, and clinical improvement was observed in 10 cases while a fairly good response was seen in one case. Of the two cases in this group that did not receive antibiotics, one-presented progressive worsening during follow up.

Cerebrospinal fluid analysis was carried out in 18 patients, 15 of which presented discrete lymphomononuclear pleocytosis with normal or slight increase in protein concentration. The lab studies of three patients demonstrated only increased protein concentration. Magnetic nuclear resonance (MR) imaging was performed in four patients, the first of which showed substantial thickening of trigeminal and facial nerves and pachymeningitis. The second lab study revealed barrier breach, the third was suggestive of Gasser gangliositis while the fourth case showed aspects of leuko-encephalopathy. One patient admitted with meningitis, facial palsy and sudden deafness had an initial normal cranial MR. However, another cerebral MR performed 5 years later, after many neurological relapse episodes, including suicide attempt, showed images suggestive of chronic encephalopathy.

Electromyography performed in a patient with significant muscle weakness displayed an inflammatory myositis pattern. Evoked potential performed in a case of facial palsy confirmed the neuritis diagnosis, and audiometry carried out in a patient with hearing impairment revealed bilateral nerve lesion.

Nine out of the 16 patients (56.3%) belonging to the early BYS group with neurological involvement, and 10 out of the 14 patients (71.4%) from the late BYS group were followed up for between two months and 13 years, with a mean period of 20.4 months. Five of the 9 patients (55.6%) belonging to the early BYS group had at least one episode of recurrence. Four patients exhibited neurological symptoms, 5 had arthritis and only one case displayed skin lesion. In contrast, 9 out of the 10 individuals (90%) from the late BYS group developed at least one episode of recurrence. Eight of these repeated neurological symptoms, 6 presented arthritis and only one case had skin lesion. The first relapsing episode took place months or years after BYS diagnosis.

Long-term follow up of 19 patients with BYS demonstrated that 14 cases (73.6%) exhibited at least one episode of recurrence, despite previous antibiotic treatment administered at the time of initial neurological manifestation. Neurological complaints were identified in 12 cases (85.7%) of relapses, arthritis in 11 (77.1%) while only two patients (14.2%) had skin lesions. Some patients presented more than one relapse episodes

and most of these had simultaneous neurological and articular (arthritis) symptoms. Importantly, the incidence of cutaneous disease became progressively lower with time, severely hampering diagnosis of late BYS in the absence of recurrent EM or secondary annular skin rash typical of the disease. This fact is of crucial importance to Brazilian physicians, since latent BYS can be misdiagnosed and confounded with idiopathic articular and neurological conditions. Moreover, the arthritis may occur both in early and late BYS groups.

The following neurological or psychiatric symptoms were found in 12 patients with BYS during relapse episodes: peripheral neuropathy in 6 patients (50%), lymphocytic meningitis in two (16.7%), cranial neuritis (sudden deafness, diplopia) in two (16.7%), psychiatric disturbance (suicide attempt, severe depression and severe emotional inconsistency) in three (25%), myopathy in two (16.7%), cognitive symptoms in three (25%) and chronic fatigue in two patients (16.7%). These results suggest that frequencies of meningitis and cranial neuritis decrease with BYS progression.

## DISCUSSION

The present study introduces new insights in BYS by timely and prospective analysis of a series of 30 patients with neurological symptoms. Firstly, the study reinforces the importance of careful epidemiological history inquiry in diagnosing this new emerging Brazilian zoonosis. Follow-up of patients who presented with initial neurological symptoms, confirmed that BYS is a distinct and completely different illness to the classical LD found in the Northern Hemisphere. The many particularities related to this zoonosis lend supports the notion that BYS is virtually a new tick borne disease and that the introduction of the name BYS was an attempt to separate it conclusively from classical LD.

In our series of neurological patients, we saw that symptoms were very similar to those exhibited by LD patients, except for the high frequency of disease recurrence and psychiatric or psycho-social disorders specific to BYS. Relapse episodes of BYS had occurred in 73.6% of patients during the mean follow up period of 20.4 months. Importantly, the frequency of characteristic skin lesions, meningitis and cranial neuritis decreased as the disease progressed. Most patients exhibited simultaneous articular and neurological compromise. EM was identified in 13 out of 30 patients (43.3%) at onset of BYS with neurological involvement. However, as the disease relapsed the frequency of skin lesions reduced (14.2%), hampering the diagnosis of late BYS. Relapse episodes occurred in almost 50% of patients diagnosed at early stages of BYS, and in

nine out of 10 patients (90%) at late stages of the disease. In general, treatment of relapse episodes with antibiotics proved efficacious, but did not prevent further recurrences.

All the classical neurological symptoms described in LD were also reported in BYS patients, including typical symptoms of the triad constituted of aseptic meningitis and/or involvement of cranial and/or peripheral nerves<sup>28,29</sup>. In general, patients with meningitis displayed few symptoms, with mild headache, low fever and absence of vomiting. Often, they were diagnosed only through cerebrospinal fluid analysis. The peripheral radiculitis were characterized by non-symmetrical pain or lesion of motor nerve with paresis. Most of the cranial nerves were affected, but oculomotor, facial and abducens nerves were the most compromised. The co-existence of multiple neurological lesions or simultaneous involvement of neurological and articular symptoms in the same patient, were the most notable diagnostic characteristics of BYS.

Encephalomyelitis, defined as unifocal or multifocal inflammatory process of the central nervous system and/or spinal cord, is reported in up to 10% of North American and European patient<sup>2,28</sup>, and sometimes confounded with symptoms present in multiple sclerosis<sup>29,30</sup>. This is a rare condition that progresses slowly with involvement of the white matter<sup>31</sup>. Transverse myelitis characterized by spinal cord vasculitis with Babinski sign and sensory level or bladder involvement, is reported in 4% of LD patients<sup>32</sup>. In our group, 10 patients (33.3%) had diagnosis of encephalomyelitis, clinically expressed by presence of seizures, cerebellar ataxia, transverse myelitis, coma, sphincter loss, and severe psychiatric disorders. Interestingly, five patients at early stages of BYS had encephalomyelitis, leading to a diagnosis confounded with multiple sclerosis.

A high frequency of psychiatric or psycho-social disorders was observed in BYS. Neuropsychiatric manifestations of LD are often under diagnosed and the first studies in this area were published by Kohler<sup>33</sup> and Omasits *et al.*<sup>34</sup> According to Kohler,<sup>33</sup> the spectrum of psychiatric manifestations range from depressive mood in early stages of the disease, organic personality disorders at mid-stage and organic psychosis, dementia and anorexia in late phases of the illness. Omasits *et al.*<sup>34</sup> included the possibility of suicidal ideas. Other psychiatric abnormalities such as personality change, depersonalization, mania, hallucinations, paranoia, catatonia, obsessive-compulsive disorder, panic attacks and disorientation have been possible to happen<sup>35</sup>. In our group of neurological cases, all BYS cases in psychiatric patients received care by specialists who reported manifestations including suicidal attempt, profound depressive state, anorexia, social disability, panic

attacks and hallucinations. A dramatic example of psychiatric involvement was seen in a woman with a prolonged history of BYS and who presented many relapsing episodes of articular and neurological symptoms. At one point she was admitted to hospital having tried to commit suicide. Psychiatric evaluation confirmed brain organic disease whereas magnetic resonance scan showed demyelinating of brain white matter.

Encephalopathy was identified in 8 patients with neurological symptoms of BYS, and was characterized by the presence of cognitive disturbances, affecting memory and causing changes in verbal fluency, attention, sleep and concentration. This condition is well documented in medical literature<sup>35</sup> and can be linked to secondary manifestation of central nervous system infection<sup>36</sup> or reflect mild form of encephalomyelitis<sup>37,38</sup>. Minor manifestations of encephalopathy are very frequent, constant and bear the symptoms reported by many BYS patients, particularly at late stages of the disease. Chronic fatigue and cognitive disturbances are common symptoms which manifest during long-term follow up of BYS. These are highly morbid manifestations that are difficult to treat.

The same antibiotics used to treat LD are employed in BYS. In general, the treatment is effective to ameliorate and shorten disease episode duration. In Brazil, neurological symptoms are treated with ceftriaxone 2 g/day intravenously or penicillin 2.4 million units/day for 30 days, with additional support by use of oral antibiotics such as doxycycline, administered for two to three months in an attempt to prevent future relapse. In Brazil, is recommended the use of sulphate of hydroxychloroquine for a prolonged period of time to avoid disease relapse and ameliorate present symptoms. Unfortunately, despite all efforts the treatment of BYS is often unsatisfactory, especially when the disease progresses with relapse episodes. Our recent data (not published) have shown the presence of auto-antibodies against neuronal antigens in almost 50% of patients, especially against those located at the cellular membrane. We remain in doubt as to whether the pathogenesis of late relapse symptoms of BYS stems from infection persistence or autoimmune disturbance.

The underlying reasons for the differences observed between the clinical pictures of BYS and LD are unknown. We assume that relapse episodes occur in BYS because the etiological agent in Brazil is very different. Our data have demonstrated the presence of atypical spirochetes, possibly in their L form (cell wall deficient bacteria) in patients with BYS (data not published). These structures are uncultivable in BSK medium, have short-lived growth in SP4 medium adequate for spiroplasmas, are poorly stained by Giemsa and acridine orange, invade endothelial cells *in vitro*, and finally, PCR tests done employing specific or conservative primers

for genus *Borrelia* are always negative. These spirochete-like structures, when examined by electron microscopy, reveal many different structures akin to cysts, blebs, dense corpuscles (like *Chlamydias*), spirochete-like non-flagellated bacteria, and microorganisms resembling *Mycoplasmas*. After many studies and literature review, we are convinced that these structures are in fact spirochetes that have lost genetic content and, consequently, expressing lower amount of bacteria proteins, like flagellum and out membrane lipoproteins.

Indeed, these recent studies done at FMUSP, corroborate and are able to elucidate most of the particularities observed in BYS. For instance they explain: 1- Why it is so difficult to grow these atypical spirochetes in different culture media; 2- Why serology against *B. burgdorferi* has low sensitivity; 3- Why PCR is negative; 4- Why BYS is a relapsing disease; 5- Why antibiotics are less effective as the disease relapses; 6- Why disease-modifying drugs such as sulphate of hydroxycloquine or methotrexate, are useful in treating chronic articular involvement in BYS.

We postulate that morphologically atypical spirochetes, etiological agents of BYS, have emerged in our country as consequence of the absence of *I. ricinus* complex ticks in Brazil. Studies conducted in high-risk areas for BYS showed presence of *Ixodes loricatus* and *Ixodes didelphidis* ticks, but these invertebrate hosts do not sting humans. However, they do participate in the transmission cycle of BYS thereby helping to maintain the circulation of spirochetes among wild animals. It is accepted that the passage of spirochetes among vertebrate and invertebrate hosts modifies its genetic and protein expression, which are necessary mechanisms for bacteria surveillance among different hosts. Finally, we believe that the absence of *I. ricinus* complex ticks in Brazil is a key factor preventing the appearance of typical helical spirochete in our country.

In conclusion, BYS replicates most of the neurological symptoms observed in LD, except for the additional presence of relapse episodes and the tendency to cause chronic neurological and articular manifestations. The understanding of BYS of interest for various disciplines of different specialties, because it is a new tick borne disease, completely different from classical LD. Furthermore, since this zoonosis relapses, progresses and develops autoimmune features, it brings serious differential diagnostic concerns with chronic idiopathic rheumatic and neurological syndromes.

## REFERÊNCIAS

### REFERENCES

1. Steere AC, Malawista SE, Snyder DR. Lyme arthritis: an epidemic of oligoarthritis in children and adults in three Connecticut communities. *Arthritis Rheum.* 1977; 20:7-17.

2. Steere AC. Lyme disease. *N Engl J Med.* 1989; 21:586-96.
3. Steere AC. Lyme disease. *N Engl J Med.* 2001; 345:115-25.
4. Azulay RD, Abulafia L, Sodre CS. Lyme disease in Rio de Janeiro, Brazil. *Int J Dermatol.* 1991; 30:569-71.
5. Talhari S, Talhari A, Ferreira LCL. Eritema migrans, eritema migratório, doença de Lyme ou borreliose de Lyme. *An Bras Dermatol.* 1992; 67:205-9.
6. Yoshinari NH, Barros PJJ, Cruz FCI, Oyafuso LK, Mendonça M, Baggio D. Clínica e sorologia da doença de Lyme no Brasil. *Rev Bras Reumatol.* 1992; 32:57.
7. Abel IS, Marzagão G, Yoshinari NH, Schumaker TTS. *Borrelia* like spirochetes recovered from ticks and small mammals collected in the Atlantic Forest Reserve, Cotia county, State of São Paulo, Brazil. *Mem Inst Oswaldo Cruz.* 2000; 95:621-4.
8. Costa IP, Bonoldi VLN, Yoshinari NH. Search for *Borrelia* sp in ticks from potential reservoir in an urban forest in the State of Mato Grosso do Sul, Brazil: a short report. *Mem Inst Oswaldo Cruz.* 2002; 97:631-5.
9. Barros-Battesti DM, Yoshinari NH, Bonoldi VLN, De Castro Gomes A. Parasitism by *Ixodes didelphidis* and *Ixodes loricatus* (Acari: Ixodidae) on small wild animals from Atlantic Forest in State of São Paulo, Brazil. *J Med Entomol.* 2000; 37:820-8.
10. Mantovani E, Costa IP, Gauditano G, Bonoldi VLN, Higuchi ML, Yoshinari NH. Introducing Lyme Disease Like Syndrome or Lyme Disease Imitator Syndrome. Is it Borreliosis or a new Brazilian Tick-borne Disease? *Braz J Med Biol Res.* 2007; 40:443-56.
11. Fonseca AH, Salles RS, Salles SAN, Madureira RC, Yoshinari NH. Borreliose de Lyme símile: uma doença emergente e relevante para a Dermatologia no Brasil. *An Bras Dermatol.* 2005; 80:171-8.
12. Yoshinari NH, Barros PHL, Gauditano G, Fonseca AH. Report of 57 cases of Lyme-like disease (LLD) in Brazil. *Arthritis Rheum.* 1999; 43:S188.
13. Yoshinari NH, Barros PJJ, Bonoldi VL, *et al.* Outline of Lyme borreliosis in Brazil. *Rev Hosp Clin Fac Med S Paulo.* 1997; 52:111-7.
14. Yoshinari NH, Barros PJJ, Fonseca AH, *et al.* Borreliose de Lyme. Zoonose emergente de interesse multidisciplinar. *Newslab.* 1995; 12:90-104.
15. Yoshinari NH, Barros PJJ, Fonseca AH. Borreliose de Lyme. Zoonose emergente de interesse multidisciplinar. *Newslab.* 1995; 12:90-104.
16. Costa IP, Yoshinari NH, Barros PJ, Bonoldi VLN, Leon EP, Zeitune AD. Lyme disease in Mato Grosso do Sul State, Brazil: Report of three clinical cases, including the first of Lyme meningitis in Brazil. *Rev Hosp Clin Fac Med S Paulo.* 1996; 51:253-7.
17. Pirana S, Yoshinari NH, Bento RF, Silveira JAM. Paralisia facial e surdez súbita bilateral na doença de Lyme. *Rev Bras Otorrinol.* 1996; 62:500-2.
18. Pirana S, Yoshinari NH, Silveira AM, Bento RF, Bonoldi B. Serological reactivity to *Borrelia burgdorferi*, *Borrelia afzelli*, and *Borrelia garinii* antigens in patients afflicted by peripheral facial paralysis in Brazil. *Otol Neurotol.* 2002; 23(Suppl 1):S33.
19. Lorenzi MC, Bittar RSM, Pedalini MEB, Zerati F, Yoshinari NH, Bento FR. Sudden deafness and Lyme disease. *Laryngoscope.* 2003; 113:312-5.
20. Sato MT, Schmitt A, Greboge P, Arana J, Moreira ATR, Yoshinari NH. Neurorretinite associada à ceratite intersticial: relato do primeiro caso de doença de Lyme no Estado do Paraná. *Res Bras Oftal.* 2003; 62:275-83.
21. Costa IP, Bonoldi VLN, Yoshinari NH. Perfil clínico e laboratorial da doença de Lyme símile no Estado de Mato Grosso do Sul: análise de 16 pacientes. *Rev Bras Reumatol.* 2001; 41:142-50.
22. Varela AS, Luttrell MP, Howerth EW *et al.* First culture isolation of *Borrelia lonestari*, putative agent of Southern tick-associated rash illness. *J Clin Microbiol.* 2004; 42:1163-9.
23. Blanton L, Keith B, Brzezinski W. Southern tick-associated rash illness: Erythema migrans is not always Lyme disease. *South Med J.* No prelo.
24. Masters EJ, Grigery CN, Masters RW. STARI, or Masters disease: Lone star tick-vectored Lyme-like illness. *Infect Dis Clin North Am.* 2008; 22:361-76.
25. Costa IP. Pesquisa de anticorpos anti-*Borrelia* e do agente etiológico, em soro e liquor de pacientes com manifestações clínicas compatíveis com a Doença de Lyme, no Estado de Mato Grosso do Sul. [tese de doutorado], São Paulo: Faculdade de Medicina de São Paulo, FMUSP; 1998.
26. Barros PJJ. Caracterização clínica e laboratorial da doença de Lyme no Brasil, através de métodos imunológicos e reação em cadeia de polimerase. [tese de doutorado], São Paulo: Faculdade de Medicina de São Paulo, FMUSP; 2000.
27. Mandell H, Steere AC, Reinhardt BN, Yoshinari NH, Munsat TL. Lack of antibodies to *Borrelia burgdorferi* in patients with amyotrophic lateral sclerosis. *N Engl J Med.* 1989; 320:255-6.
28. Pachner AR, Steere AC. The triad of neurologic manifestations of Lyme disease: meningitis, cranial neuritis, and radiculoneuritis. *Neurology.* 1985; 111:47-53.
29. Kristoferitsch W. Neurological manifestations of Lyme borreliosis; clinical definition and differential diagnosis. *Scand J Infect Dis Suppl.* 1991; 77:64-73.
30. Schmutzhard E. Multiple sclerosis and Lyme borreliosis. *Wien Klin Wochenschr.* 2002; 114:539-43.
31. Stanek G, Strle F. Lyme borreliosis. *Lancet.* 2003; 362:1639-47.
32. Hansen K, Lebech AM. The clinical and epidemiological profile of Lyme neuroborreliosis in Denmark 1985-1990. *Brain.* 1992; 115(Pt2):399-423.
33. Kohler VJ. Lyme disease in neurology and psychiatry. *Fortschr Med.* 1990; 108:191-4.
34. Omasits M, Seiser A, Brainin M. Recurrent and relapsing borreliosis of the nervous system. *Wien Klin Wochenschr.* 1990; 102:4-112.
35. Fallon BA, Nields J. Lyme disease. A neuropsychiatric illness. *Am J Psychiatry.* 1994; 151:1571-83.
36. Halperin JJ, Logigian EL, Finkel MF, Pearl RA. Practice parameters for the diagnosis of patients with nervous system Lyme borreliosis (Lyme disease). *Neurology.* 1996; 46:619-27.
37. Logigian EL, Kaplan RF, Steere AC. Chronic neurologic manifestations of Lyme disease. *N Engl J Med.* 1990; 323:1438-44.
38. Kaplan RF, Meadows ME, Vincent LC, Logigian EL, Steere AC. Memory impairment and depression in patients with Lyme encephalopathy; comparison with fibromyalgia and non-psychotically depressed patients. *Neurology.* 1992; 42:1263-7.