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Baggio-Yoshinari syndrome: a literature review

Síndrome de Baggio-Yoshinari: uma revisão da literatura

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ABSTRACT: Baggio-Yoshinari Syndrome (BYS) is an emergent Brazilian zoonosis that presents similarities with Lyme disease (LD), differing in some clinical and immunological aspects. Both diseases are caused by *Borrelia Burgdorferi sensu lato*, spirochetes transmitted to the vertebrate host by tick bites. In this study, an integrative review was aimed about the BYS, abranging large aspects like diseases history, clinical manifestations, immune events, diagnostic and treatment. A bibliographic survey was conducted in PubMed/MEDLINE, Scielo, Science Direct, Lilacs e Bireme databases, where 25 scientific articles were extracted for analysis, without temporal delimitation. It was evidenced the large geographical and biological diversity of Brazil contributed to the occurrence of changes in *B. burgdorferi* that results in SBY particularities. The bacterium, helped by proteins of the tick saliva can overcome immunological barriers to complete the infection. Initially, the diagnosis is based on the presence of oligoarthritis, and neurological, dermatological, cardiac or ocular symptoms may also be present, followed by the assessment of other clinical and laboratory criteria. The treatment consists in the use of doxycycline or amoxicillin associated with other drugs according to the clinical manifestations. The results suggest that SBY, despite the low number of studies about this pathology, is configured like an emerging disease that needs more attention from the scientific community to permit early disease diagnosis avoiding chronic events in the patients.

Keywords: Tick-Borne Diseases; *Borrelia burgdorferi*; Spirochaetales; Zoonoses; Ticks.

RESUMO: A Síndrome de Baggio-Yoshinari (SBY) é uma zoonose emergente brasileira que apresenta semelhanças com a doença de Lyme (DL). Ambas são causadas pela espiroqueta *Borrelia burgdorferi sensu lato*, transmitida para hospedeiros vertebrados por meio de picadas de carrapato. Contudo, a SBY diverge da DL em alguns aspectos clínicos e imunológicos. No presente estudo, objetivou-se realizar uma revisão integrativa da literatura sobre a SBY, abordando aspectos amplos como história da doença, epidemiologia, manifestações clínicas, aspectos imunológicos, diagnóstico e tratamento. Foi realizado um levantamento bibliográfico nas bases de dados PubMed/MEDLINE, SciELO, Science Direct, LILACS e Bireme, de onde foram extraídos 25 artigos científicos para análise, sem delimitação temporal. Evidenciou-se que a grande diversidade biológica e geográfica do país contribuiu para a ocorrência de modificações na *B. burgdorferi* que, possivelmente, resultaram nas particularidades da SBY. A bactéria, auxiliada por proteínas da saliva do carrapato, consegue transpor as barreiras imunológicas do hospedeiro para infectá-lo. Inicialmente, o diagnóstico baseia-se na presença de oligoartrite, podendo também estar presentes sintomas neurológicos, dermatológicos, cardíacos ou oculares, seguindo-se com a avaliação de outros critérios clínicos e laboratoriais. O tratamento consiste na utilização de doxiciclina ou amoxicilina associada a outros fármacos de acordo com as manifestações clínicas. Nota-se que a SBY, apesar de pouco estudada, configura-se como uma doença emergente que necessita de maior atenção por parte dos setores de saúde pública e da comunidade científica para melhor caracterização do quadro clínico e, consequente realização de diagnóstico precoce, evitando acometimentos crônicos aos pacientes.

Descritores: Doenças transmitidas por carrapatos; *Borrelia burgdorferi*; Espiroqueta; Zoonoses; Carrapatos.

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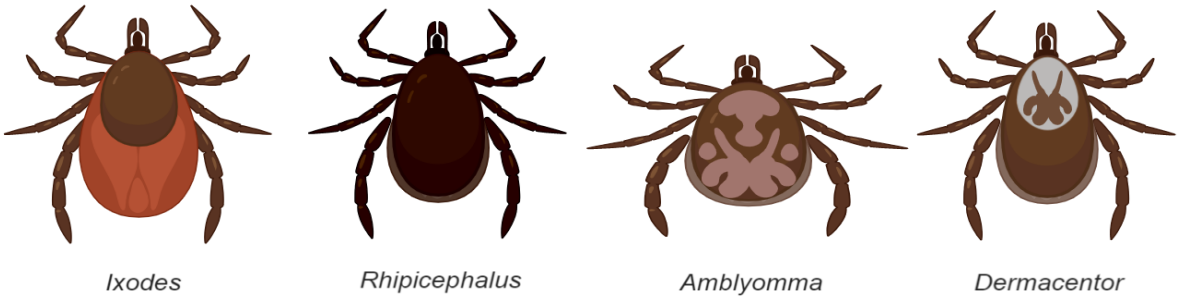
INTRODUCTION

Baggio-Yoshinari Syndrome (BYS), also known as Brazilian Lyme-like disease, Lyme borreliosis or Brazilian borreliosis[1,2], is an emerging Brazilian zoonosis with the first case report was dated in 1992, in the city of São Paulo, Brazil[3-5]. It is similar to Lyme disease (LD), a typical disease in the northern hemisphere, presenting all the classic clinical manifestations of LD, but it differs in terms of the frequency of autoimmune episodes and events[6-8].

Both are known to be caused by the spirochete *Borrelia burgdorferi sensu lato*, a bacteria classified as gram-negative, but which does not produce lipopolysaccharide (LPS)[1,9]. However, it is speculated that BYS is caused by a genetically modified *B. burgdorferi* strain, with mutations in the *flg*E gene (responsible for the synthesis of flagellar structure) and the *fla*B gene (the main flagellin gene), which makes the spirochete assume an atypical morphology. From this perspective, it is assumed that the different geographical conditions of Brazil, combined with the great Brazilian biodiversity, mainly the existence of exotic species of ticks and other natural reservoirs, have contributed to the evolutionary adaptation of the pathogen in the country. Corroborating these investigations, it is described that the spirochetes found in the blood of patients with BYS are in their "L" form, characterized by the presence of a deficient cell wall, loss of flagella and with atypical morphology with a vegetative presentation, a characteristic probably resulting from changes due to unfavorable survival conditions[3,6,9-15].

The bacteria has a zoonotic cycle in which ticks of the type *Ixodes*[2] are usually included. But in Brazil, according to Gonçalves et al.[2] and Mantovani et al.[11] it was shown that these spirochetes are also present in ticks of the type *Rhipicephalus*, *Amblyomma* and *Dermacentor* (Figure 1), which transmit to dogs, horses, marsupials, rodents, opossums, cattle and humans[1,16-19]. *B. burgdorferi* infects ticks when they feed on the blood of infected hosts [1]. However, despite the confirmation by serological techniques of the existence of this infection in humans and animals, the culture and isolation of *B. burgdorferi* has not yet been successfully performed in Brazil[9,10].



Source: Own authorship, 2019.

Figure 1. Graphic representation of exemplos of ticks type *Ixodes*, *Rhipicephalus*, *Amblyomma* and *Dermacentor*

After being bitten by an infected tick, skin lesions may occur[20,21]. However, not all individuals become ill and the host may be presented as an asymptomatic carrier of the bacteria for years[10,20]. In the event of symptoms, the host may develop broad-spectrum clinical manifestations, such as neurological, joint, cardiac or ocular dermatological symptoms[7,8,20]. More recently, Costa and Yoshinari[7] describe that patients with BYS may also present clinical manifestations similar to autoimmune diseases, such as dry syndrome, inflammatory arthritis, idiopathic myositis, panniculitis, skin lesions compatible with scleroderma, vasculitis, antiphospholipid antibody syndrome and the occurrence of manifestations observed in systemic lupus erythematosus (SLE), such as Raynaud's phenomenon, photosensitivity, butterfly wing injury and alopecia. Also, triggering or worsening of allergic processes to drugs or food may occur.

Concerning the laboratory alterations, the production of antibodies against autologous cellular components produced during the clinical evolution of the disease is noted, nevertheless, there are still few studies that address this theme[1,3]. The main changes reported by Costa and Yoshinari[7] refer to the presence of ACF (anti-core factor), anti-Ro/La, anti-cardiolipin IgG/IgM, anti-neutrophil cytoplasm, neuronal and cutaneous anti-constituent antibodies, hypergammaglobulinemia and, in some cases, the elevation of IgE.

In view of the scarcity of studies, analyzes of aspects of BYS such as the history of the disease, epidemiology, clinical manifestations, immunological aspects, diagnosis, and treatment become relevant, as they broaden the discussion on the topic, in order to better understand this emerging disease in human beings. Therefore, the objective of the study was to conduct a literature review about aspects of the syndrome, with an emphasis on the clinical and immunological manifestations of BYS.

METHODS

It is an integrative literature review, since it contributes to the process of systematization and analysis of results, allowing the understanding of a certain theme. After elaborating on the research question, a bibliographic survey was made in the databases PubMed/MEDLINE, SciELO, Science Direct, LILACS, BIREME, using the following descriptors: "Baggio-Yoshinari", "*Brazilian borreliosis*", "Brazilian Lyme-like", without time delimitation, in English or Portuguese. The exclusion criteria were: theses, monographs, not available in their entirety, and research carried out with experimental models (rats and/or mice).

In the last step to analyze and compile the results, 17 abstracts/articles were carefully read in order to organize and tabulate the data. Subsequently, due to the need for theoretical complementation of the specificities of the theme, the descriptor "*Borrelia burgdorferi tick Brazil*", "*Borrelia burgdorferi*" was added to the PubMed/MEDLINE and SciELO database, also without temporal delimitation. After applying the exclusion criteria, three original articles were identified in the respective databases. In addition to these, after a manual search, five articles were included in the final analysis, due to the thematic relevance about the object of study of this review. For the organization and tabulation of data, a complete reading of 25 works was carried out, selected from a total of 1.307 publications (Figure 2).

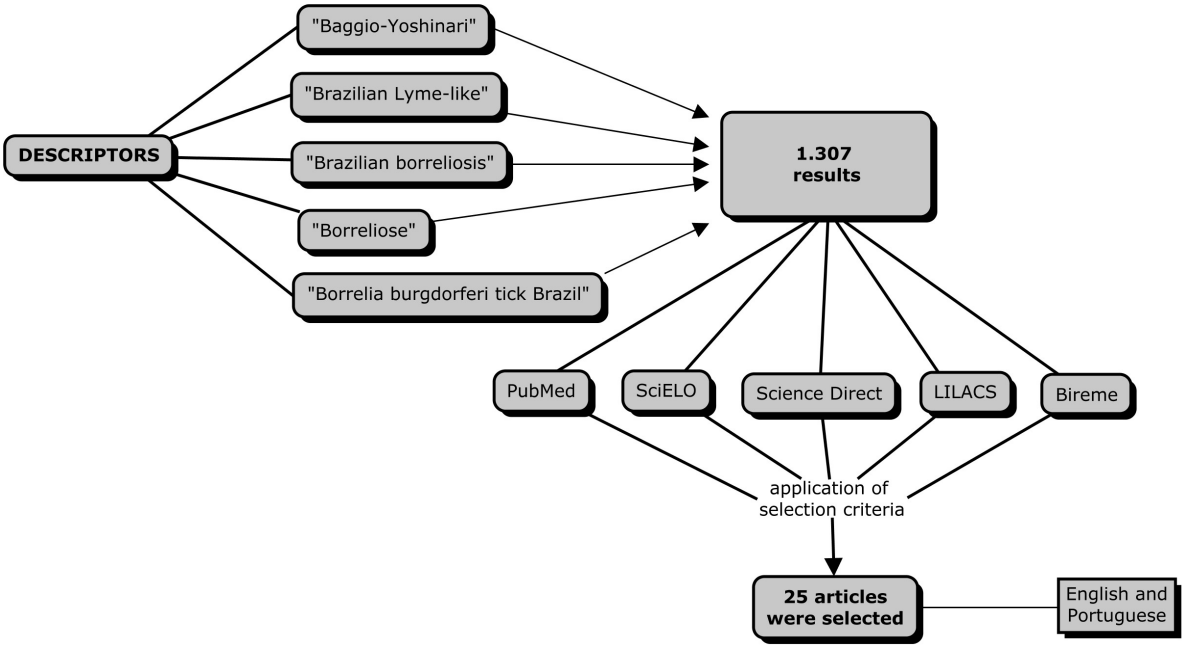


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Figure 2. Flowchart for the selection of scientific articles on Baggio-Yoshinari Syndrome

RESULTS AND DISCUSSION

History of the disease and epidemiology

BYS was first described in Brazil in 1992, in the city of Itapevi, São Paulo. Two brothers were diagnosed after having a history of tick bite and subsequent development of fever, migratory erythema and arthritis[4,5,10,19,20,22]. However, there are case reports from 1988, in Rio de Janeiro, there was no description of clinical and laboratory symptoms. Subsequently, some cases were identified in humans and animals, by serological methods in Espírito Santo, Rio de Janeiro, São Paulo, Minas Gerais and Mato Grosso do Sul, Amazonas, Tocantins and Paraná, showing a large geographical distribution area for this infection[3,16,23,24]. According to Dall'Agnol et al.[22], from 2009 to 2016, 4.078 suspected cases of BYS were recorded in Brazil. A number of 679 of these cases had serological confirmation for the presence of *B. burgdorferi*. The number of identified cases reinforces the need to create surveillance strategies and actions. However, as reported by Gonçalves et al.[2], BYS still has a poorly characterized epidemiology due to the lack of studies on this disease.

Studies such as those by Melo et al.[16], by Montandon et al.[17], and Nascimento et al.[18], demonstrated that wild and domestic animals present serological evidence of infection by *B. burgdorferi*. Samples of dogs, horses, marsupials, rodents and opossums, analyzed in these studies, showed positive serology for antibodies anti-*B. burgdorferi*.

The majority of cases in human beings have been identified in inhabitants of rural areas, where the incidence of this zoonosis is high due to the proximity

to animals parasitized by ticks[2]. It is understood that the rural environment is the most favorable for the vector because of the generally inadequate sanitary conditions, climate and favorable environment. It is admitted that infections transmitted by tick bites are common in Brazil, due to their wide geographical distribution in the Brazilian territory[12]. Furthermore, the study by Passos et al.[20] revealed a positive association between the appearance of cutaneous manifestations related to infection in the summer and autumn seasons. This is probably due to the rainy season in Brazil that occurs in the months from October to March, in which the infectious forms of ticks are present in nature due to their evolutionary cycle, as they develop at temperatures below 28ºC/ 82,4º F.

Clinical manifestations

B. burgdorferi found in Brazil presents differences that are considered responsible for the particularities in the clinical manifestation of BYS in relation to LD. Some authors suggest that the atypical cystic morphology of the bacteria, without periplasmic flagellum and with a decrease in the expression of external surface proteins (Osp), may justify the particularities of this strain, which may impact on the presentation of signs and symptoms by the host[1,7,10,15].

In Brazil, BYS can have a long incubation period, ranging from months to years [25]. A study by Gouveia et al.[10], indicates variation from one day to six years between the tick bite and the appearance of the first clinical manifestations. Clinically, BYS can be divided into acute and/or recurrent latent stage (Figure 3). If the onset of signs and symptoms occurs within three months, it is defined as an acute stage of the disease[10]. At this stage, at the location of the bite in the vertebrate host, an initial lesion of the primary phase of the disease may appear, which is due to the inoculation of the infectious agent, constituting the chronic migratory erythema (CME). This is a characteristic clinical sign that presents itself as an exanthema associated with the increase in local temperature, progressing in a centrifugal way and evolving towards the formation of rings; however, variations can occur, such as triangular shapes or the appearance of erythematous plaques. CME can disappear without treatment and reappear in a localized or disseminated form about a month after the bite, a period that constitutes the secondary stage of the disease. This manifestation may be recurrent for years or may be absent in patients with BYS[12,20,23]. However, in some cases, it is observed that there is no manifestation of the acute stage. Given this fact, it is plausible to consider that individuals infected with *B. burgdorferi* can progress directly to the recurrent latent stage, which can last for years. In these cases, the host presents itself only as a carrier of the bacteria, so that, at a given point in life, the loss of immunity may result in a wide range of symptoms[7,8].

It is important that the diagnosis and treatment are established in the acute stage, avoiding irreversible sequelae and the evolution of chronic rheumatic, and neurological conditions[10]. In addition to cutaneous manifestations, this zoonosis includes osteoarticular, neurological, cardiac, psychiatric, ocular and immuno-allergic symptoms in its clinical spectrum[7,8,12]. The rheumatic condition of BYS usually affects large joints, such as the knee, with the occurrence of oligoarticular symptoms in approximately half of the patients at the beginning of the disease or during episodes of relapse. Studies indicate that the majority of patients with joint involvement also have some neurological impairment[6,25].

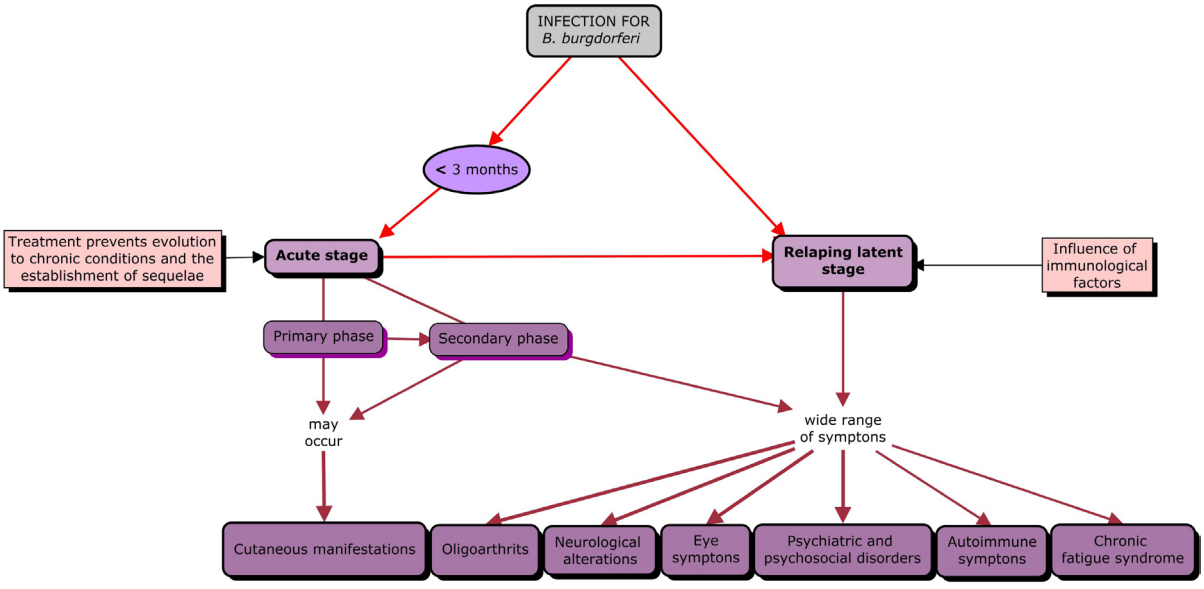

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Figure 3. Natural history of Baggio-Yoshinari syndrome

Neurological alterations can be present in both the acute and latent stages of the disease and usually occur with the association of multiple symptoms. In the acute phase, the occurrence of meningism is evident, present in approximately half of the patients, associated, in most cases, with fever, nausea, vomiting and neck pain. Some patients have peripheral motor radiculitis, which triggers lesions mainly on the oculomotor, abducent and facial nerves; peripheral sensitive radiculitis; peripheral facial nerve palsy; and ocular symptoms, with retinal arteritis, optic neuritis and uveitis being the most common and serious complications; even though ocular disorders are not typical of BYS, they can affect up to 35% of patients[6-8,12,20].

In addition to these changes, studies report the occurrence of psychiatric and psychosocial disorders in patients without a history of psychiatric illnesses. There are reports of cases in which the development of aggressive behavior and severe depression occurred, including suicidal ideation, lack of appetite and social withdrawal. Besides, some cases have been described in which patients had cognitive disorders that, despite not having specific symptoms, mainly include memory loss, language disorders and sleep disorders[6]. Therefore, the importance of psychological/psychiatric monitoring for patients diagnosed with BYS is emphasized, due to the possibility of these individuals to develop psychiatric manifestations of great repercussions.

According to the study by Kowacs et al.[26], the occurrence of chronic headache occurs in association with the involvement of cranial nerves, eye diseases or temporal arteritis. However, the diagnosis of headache associated with BYS is difficult because of the appearance, generally, in the latent phase of the disease, in addition to being easily confused with primary headache chronicity or associated with the abuse of analgesics.

Immunological aspects

The tick comes into contact with *B. burgdorferi* when it feeds on an infected host. The bacteria migrate from the midgut to the salivary glands, mediated by Outer Surface Protein C (OspC), a protein expressed by this pathogen. Then, it is transported along with the spittle to the vertebrate host. It is recognized by several immune response mechanisms, such as the complement system (CS) and innate immunity cells. The recognition of *B. burgdorferi* by dendritic cells leads to the maturation of these cells and transcription of genes responsible for the expression of chemokines, apoptosis inhibitors, matrix metalloproteases and a wide spectrum of cytokines, including inflammatory mediators, neutrophil attractants and immunomodulatory cytokines. After the presentation of antigen by dendritic cells, the auxiliary CD4+ T cells Th1 and Th2 initiate the adaptive response, promoting the release of interferon-gamma (IFN-γ) and interleukin 4 (IL-4), respectively, which are related to the acute phase manifestations. Subsequently, the cytokines released by CD4 + T lymphocytes induce the proliferation and differentiation of B lymphocytes and the production of antibodies[1].

The CS also participates in defenses against the bacteria and is activated by the classic route, the alternative route and the lectin route in the presence of *B. burgdorferi* infection. One of the CS's mechanisms of action consists of the formation of pores in the spirochete envelope, through the action of the membrane attack complex (MAC), which through fragments C5b, C6, C7, and C8 and one or more molecules of C9, promote the formation of pores on the bacterial surface. The pores formed by MAC allow the influx of water and ions into the bacteria, which leads to their lysis by osmotic pressure. In addition, antibodies of the type IgG opsonize, that means, recover and promote their phagocytosis by binding the Fc receptors present in phagocytes[27].

In spite of that, the pathogen uses mechanisms, during its transmission and dissemination, to evade and modulate the host's innate and adaptive immune responses (Figure 4). It is known that there are salivary proteins of the tick that are able to help *B. burgdorferi* to circumvent the body's defenses, with immunosuppressive, anti-complement and anti-hemostatic activity. In this context, Salp15, a salivary protein induced by tick feeding, inhibits the activation and proliferation of CD4 T^+ lymphocytes specifically binding to the CD4 co-receptor of T cells. In addition, it interacts with the bacteria by binding to OspC, providing protection against antibodies and improving the survival of the pathogen after contact with the host. Furthermore, there are salivary proteins that inhibit B lymphocytes, dendritic cells, *natural killer* cells (NK), neutrophils and macrophages. Isac and Salp20 are two other proteins in tick spittle that inhibit the alternative pathway of CS activation. In addition, *B. burgdorferi* is able to suppress the activation of CS by the expression of complement regulatory proteins in its extracellular membrane, such as CRASPs (*Complement Regulator Acquiring Surface Proteins*)[27] (Figure 5). In a study by Schuijt et al.[27], in which the action of Salp15 for direct death protection by CS is described, it is reported that the inactivation of this defense mechanism is possibly crucial for the establishment of *B. burgdorferi* infection in the vertebrate host, as CS is constituted as an important strategy of the host's immune system.

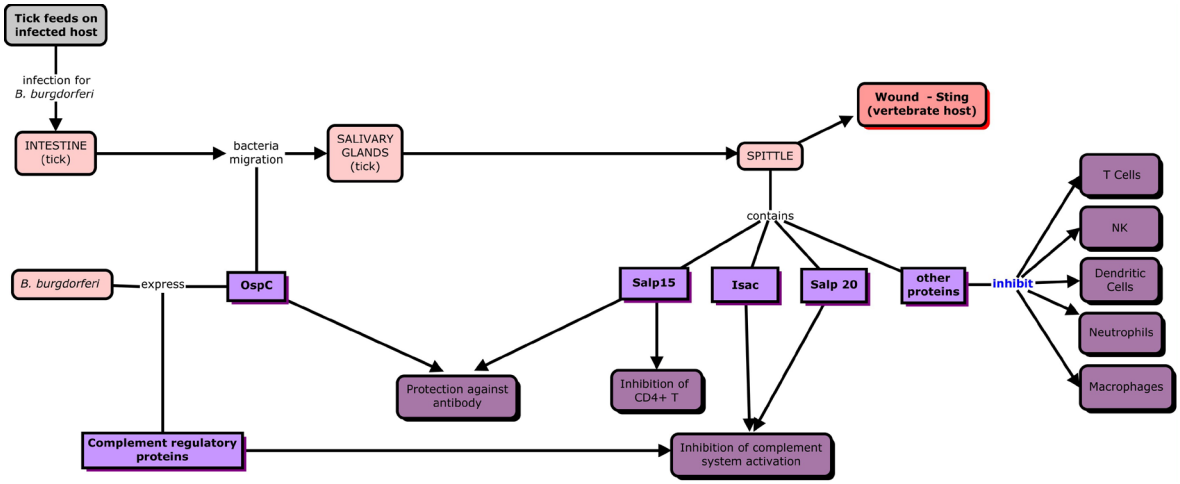

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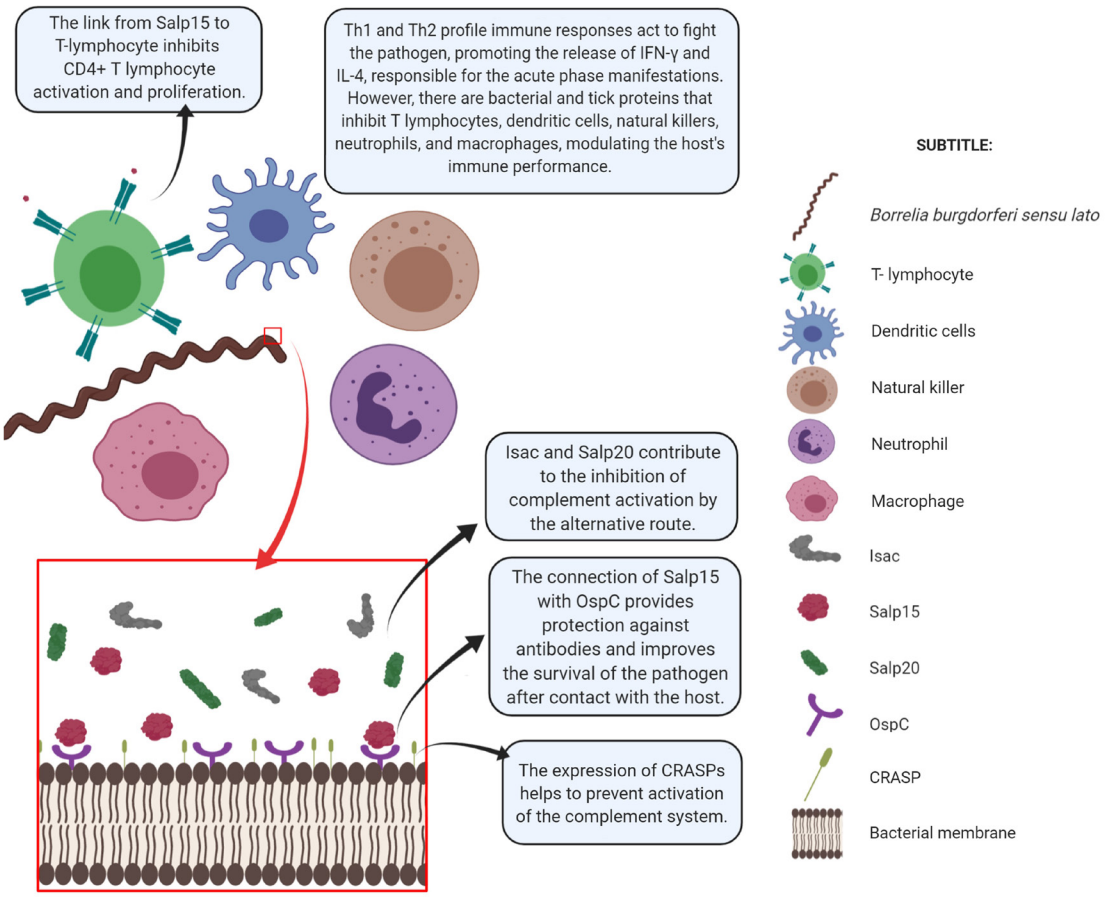
Figure 4. *B. burgdorferi* infection process and escape mechanisms from host response



Source: Own authorship, 2020.

Figure 5. Immune response to infection by *B. burgdorferi*

Diagnosis

In Brazil, whenever the individual develops oligoarthritis of large joints a BYS research is accomplished, analyzing epidemiological and clinical antecedents. However, the BYS hypothesis should be considered not only in cases of oligoarthritis but in the occurrence of any of the systemic symptoms of zoonosis and/or in individuals who present epidemiology compatible with the tick bite or onset of symptoms after visiting the risky areas.

The major parameters for diagnosis are: 1) positive epidemiology, 2) migratory erythema or systemic symptoms, such as ophthalmic, articular, neurological and cardiac manifestations, and 3) positive serology for *B. burgdorferi*. Serological confirmation is relevant, but due to the low specificity and sensitivity of serological tests in Brazil, the occurrence of false negatives and false positives are observed. As reported by Costa and Yoshinari[7], the tests carried out at the Faculty of Medicine of the University of São Paulo present a frequency of positive results in 64.7% of patients with BYS and in 16% of those not infected; therefore, they conclude that this serology in the country is not useful as a screening procedure and care should be taken when using it as a diagnostic criterion. According to the authors above, in addition to Basile et al.[1], the reason for the low specificity and sensitivity of the serological tests performed for the diagnosis of BYS is that, in these procedures, *B. burgdorferi sensu stricto, B. garinii or B. afzelii* antigens are used to evaluate immunoglobulins of *B. burgdorferi senso lato* found in Brazil.

As a minor group of parameters is considered: 1) history of systemic episodes compatible with BYS, 2) symptoms of chronic fatigue syndrome (CFS), 3) autoimmunity disorders[7,14,20,25]. A positive BYS case is considered in the presence of three major parameters or two major and two minor. The disease is not a case of compulsory notification in Brazil, as it is not lethal in the acute phase. However, there are great financial costs to treat damage related to recurrent symptoms of the latent stage, caused, in most cases, by late diagnosis[10].

The follow-up of several patients diagnosed with BYS allowed the characterization of two entities for the reaction manifestations: symptomatology compatible with CFS and another that concerns complications related to the malfunctioning of the immune system. During the evolution of BYS, patients may present symptoms compatible with autoimmune diseases. CFS, on the other hand, is an organic and acquired disease that manifests itself with neurological and immunological disorders, deficient energy production and inadequate cellular ion exchange, from the involvement of the spinal cord, and the central and peripheral nervous systems[7]. In view of this, it is possible to understand the difficulty in diagnosing patients with BYS, as this is configured as a complex disease in which the affected individual can develop several clinical and laboratory conditions as a way of progressing the disease.

Treatment

The treatment of BYS is not always satisfactory, especially if there is a delay in the clinical diagnosis. Antibiotic therapy is the same used in the treatment of classic DL, differing in terms of treatment time, which should be longer than three months when there is a delay in diagnosis[1,6,7]. The correct treatment is essential to avoid recurrence episodes since in Brazil patients who do not receive adequate treatment in the acute phase have a recurrence of symptoms in 75% of cases[7,8,11]. It is worth mentioning that the recurrence episodes are the most difficult to have therapeutic success, as there are cases of infectious recurrence and other patients who develop CFS symptoms and/or related to autoimmune diseases[7,8,10]. Thus, it is clear that, despite the efforts and achievements achieved, the treatment of BYS is not satisfactory in all cases, as BYS is not a single disease, but a constellation of complex infectious and reactive symptoms triggered by *B. burgdorferi*.

In the acute stage, doxycycline 100 mg is used twice daily for four weeks[10,12,26] or amoxicillin 500 mg, four times a day, for four weeks[10]. For patients diagnosed in the latent stage, prolonged use of doxycycline 100 mg twice a day for three months is recommended[12,26].

To treat neurological manifestations, ceftriaxone 2 g/day/intravenous or penicillin 2.4 million units/day/intravenous for 30 days is used, complemented by the use of oral antibiotics such as doxycycline (100 mg), administered twice a day for two to three months, which has the function of preventing future episodes of recurrence[6,10,12,26].

For cases of persistent joint pain even after treatment with the aforementioned options, there are reports of success when administering sulfasalazine 2 g/day or hydroxychloroquine 400 mg[26]. Antimalarial drugs have also been shown to be a useful drug as an immunomodulatory agent, helping to fight the inflammatory process, caused by inflammation and autoimmunity[7,10,14]. Unfortunately, there are no descriptions in the medical literature or references about the effective therapeutic approach to CFS, a relatively common complication in BYS.

CONCLUSION

Based on the information presented, it is noted that BYS is an emerging disease that deserves attention from the Public Health System and the scientific community. Despite the similarities with LD, which make the differentiation between the two zoonoses difficult, BYS has some particularities, such as progression to chronic events and the appearance of irreparable sequelae for the patient. We emphasize the need for further studies related to the implications of the Brazilian strain on clinical manifestations, and the development of more effective diagnostic methods and drugs in the treatment of BYS.

Conflicts of interest: No conflicts of interest, financial or otherwise, are declared by the authors.

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Authors' participation: *Silva VS, Santana MM, Gomes DLX, Medeiros EP* – Project planning, data collection and analysis process, and the preparation and review of the manuscript. *Cordeiro MF, Takenami I* – Scientific guidance, preparation of the manuscript and review.

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