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Case report

Chronic lymphomonocytic meningoencephalitis, oligoarthritis and erythema nodosum: report of Baggio-Yoshinari syndrome of long and relapsing evolution☆

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ABSTRACT

The Brazilian human borreliosis, also known as Baggio-Yoshinari Syndrome (BYS), is a tick-borne disease but whose ticks do not pertain to the Ixodes ricinus complex. It is caused by Borrelia burgdorferi sensu lato microorganisms and resembles clinical and laboratory features of Lyme disease (LD). BYS is also distinguished from LD by its prolonged clinical evolution, with relapsing episodes and autoimmune dysfunction. We describe the case of a young female who, over one year, progressively presented with oligoarthritis, cognitive impairment, menigoencephalitis and erythema nodosum. Diagnosis was established by means of the clinical history and a positive serology to *Borrelia burgdorferi sensu strictu*. The patient received Ceftriaxone 2 g IV/day during 30 days, followed by 2 months of doxicycline 100 mg bid. Symptoms remitted and the *Borrelia* serology tests returned to normality. BYS is a new disease described only in Brazil, which has a raising frequency and deserves the attention from the country´s medical board because of clinical, epidemiological and laboratory differences from LD. Despite the fact that it is a hard-to-diagnose zoonosis, it is important to pursuit an early diagnosis because the symptoms respond well to antibiotics or it might be resistant to treatment and may evolve to a chronic phase with both articular and neurological sequelae.

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Meningoencefalite linfomonocitária crônica, oligoartrite e eritema nodoso: relato de síndrome de *Baggio-Yoshinari* de longa e recorrente evolução

Palavras-chave:
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Infecções por *Borrelia*
Brasil
Spirochaetales
Doenças transmitidas por carrapatos

RESUMO

A borreliose humana brasileira, também conhecida como Síndrome de Baggio-Yoshinari (SBY), é uma enfermidade infecciosa própria do território brasileiro, transmitida por carrapatos não pertencentes ao complexo *Ixodes ricinus*, causada por espiroqueta do gênero *Borrelia* e que apresenta semelhanças clínicas e laboratoriais com a Doença de Lyme (DL). A SBY distingue-se da DL por apresentar evolução clínica prolongada, com episódios de recorrência e importante disfunção autoimune. Descreveremos o caso de uma paciente jovem, que desenvolveu progressivamente durante cerca de um ano oligoartrite de grandes articulações, seguida de distúrbio do cognitivo, meningoencefalite e eritema nodoso. O diagnóstico foi firmado devido à concomitância de queixas articulares e neurológicas com sorologia positiva para *Borrelia burgdorferi sensu stricto*. A paciente foi medicada com ceftriaxone 2 g/EV/dia por 30 dias, seguido de dois meses de doxiciclina 100 mg duas vezes ao dia. Houve remissão dos sintomas e normalização dos exames sorológicos para a borreliose. A SBY é uma zoonose emergente descrita apenas no Brasil, cuja frequência tem crescido bastante, e que, em razão das importantes diferenças nos aspectos epidemiológicos, clínicos e laboratoriais em relação à DL, merece especial atenção da classe médica do país. Trata-se de zoonose camuflada e de difícil diagnóstico, mas este deve ser perseguido com tenacidade, pois a enfermidade responde aos antibióticos no estágio inicial, podendo evoluir com sequelas neurológicas e articulares nos casos reconhecidos tardiamente ou recorrentes.

Introduction

Brazilian human borreliosis or Baggio-Yoshinari Syndrome (BYS) is an endemic anthropozoonosis proper to Brazil, caused by spirochetes of the genus *Borrelia*, transmitted by ticks of the genus *Amblyomma* and *Rhipicephalus*, which have clinical similarities with Lyme disease (LD).[1-8] BYS can be distinguished from LD, since the transmission vectors for this latter disease belong to the *Ixodes ricinus* species. Furthermore, from a clinical standpoint, this Brazilian disease evolves with symptomatic and immunological disorder recurrence.[1,5-7]

Researchers at the Medical Research Laboratory, Medicine School, Universidade de São Paulo (LIM -17) suggest that the biodiversity conditions particular to the Brazilian territory, such as the presence of exotic vectors and favorable ecological conditions, have allowed for bacteria of the *Borrelia burgdorferi* complex *sensu lato*, to adapt to the country[1,6,7,9] and develop a zoonosis with typical clinical and laboratory aspects.

The dissemination of clinical and laboratory knowledge about BYS has been a great challenge, because even with a different clinical and laboratory picture of LD, there is huge resistance from national and international scholars to admit the existence of this Brazilian zoonosis. Concepts such as prolonged latent infection caused by spirochetes in the form of cysts, clinical recurrence, different serologic diagnosis from standards adopted by the Centers for Disease Control and Prevention (CDC), and the therapeutic strategies for use of antibiotics during extended periods of time are not acceptable for certain countries of the northern hemisphere.

However, to deny its existence as an emerging clinical entity would be gross negligence, especially when there is evidence that the disease may progress to develop severe joint and neurological sequelae, if not treated properly.[6,10] In this paper, we describe an illness of prolonged evolution and recurrent symptoms, in that the diagnosis of BYS was established after the onset of meningoencephalitis with positive serology for *B. burgdorferi*, according to LIM-17 adopted standards.

Case report

Female, 35 years old, white, coming from the city of Cotia, São Paulo, where she lives since childhood. At 23, the patient showed additive polyarthritis, affecting hands, elbows, shoulders, knees and ankles. She recounts being treated with benzathine penicillin after hypothesis of rheumatic fever; however, due to the persistence of symptoms, she sought a rheumatologist who diagnosed rheumatoid arthritis, being treated with sulfasalazine, with improvement. She ceased medication after five years of clinical remission. She denied having erythema migrans (EM) and an infectious or surgical history. In June 2006 the patient displayed arthritis in her knees and left ankle, with erythematous spots on her legs. The case evolved to slow logical reasoning, amnesia for recent events, nervousness, depression and difficulty planning activities, dysgraphia, loss of balance and appearance of intermittent diplopia episodes with an increasing visual impairment. She reported febrile episodes (unmeasured). The patient lives in an urban area with dogs at home, but always goes to a farm in Ibiuna, Sao Paulo, where horses and cows are raised. The patient did not recall tick bites in the past 12 months, but relates that it had occurred several times before.

In December 2006 the patient was admitted for evaluation of cerebellar ataxia and neuritis of the 2nd cranial nerve. On admission, she was in good general condition, pale, normotensive and afebrile, without lymphadenomegaly. Upon inspection, the patient had hyperchromic macules, with palpable nodules in the anterior region of both legs, with no other mucocutaneous lesions. Cardiopulmonary and abdominal workup revealed no changes.

Arthritis showed up on her knees and left ankle, with preservation of small joints, without joint limitation or deformities.

The patient was lucid and oriented in time and space, alert and cooperative, amnesic to recent events, but with remote memory preserved. A nontoxic march with grade V driving force in all members was observed, with a mild dysmetria of the left arm. Sensitivity and reflexes were preserved and there was no sign of meningeal irritation.

Laboratory tests revealed normocytic and normochromic anemia, erythrocyte sedimentation rate = 85 mm/1st hour and C-reactive protein = 99 mg/L. The tuberculin test was negative, as well as antinuclear and rheumatoid factors. A CSF analysis revealed pleocytosis at the expense of lymphomonocytic cells. Search for infectious and parasitic agents (toxoplasmosis, tuberculosis, hepatitis B and C, herpes simplex, cytomegalovirus, cysticercosis, HIV, HTLV, mumps, cryptococcosis, trypanosomiasis, malaria) were negative in serum and CSF. The magnetic resonance imaging revealed enlargement of the basal cisterns, with a hyperintense signal on T2 and FLAIR at cerebral white matter, in the precentral gyrus at the left and in orbital gyrus at the right, without anomalous impregnation after the contrast.

Spontaneous neurological improvement was noted; afterwards, the patient was referred for outpatient follow-up. The CSF samples confirmed the diagnosis as chronic lymphocytic meningoencephalitis (Table 1).

In April 2007 the patient had intermittent episodes of diplopia and skin lesions, whose biopsy showed chronic septal panniculitis consistent with erythema nodosum. Serology for *B. burgdorferi* was requested, including ELISA IgM/IgG 1/800 reagent negative and a Western blot that revealed presence of one IgM band and 3 IgG bands.

Given the clinical laboratory and epidemiological characteristics, the diagnosis of BYS was established. Ceftriaxone 2 g/day for 30 days was introduced, followed by doxycycline 200 mg/day for two months. There was improvement in the cognitive dysfunction at the end of the first cycle of antibiotics, with disappearance of erythema nodosum and arthritis resolution. Due to the persistence of cerebellar dysfunction, the patient was readmitted for investigation in July 2007.

The neurological examination revealed decreased speed of movement to the left, dysdiadocokinesia, intention tremor and nystagmus evoked to the left. The neuropsychological assessment showed impairment in information processing as well as nominative and visual-spatial difficulties. Then, we decided to prescribe five days of pulse therapy with methylprednisolone 1 g, followed by five days of prednisone 60 mg/day. Doxycycline was maintained for 60 days, in association with 250 mg of chloroquine diphosphate. The serology for *B. burgdorferi* became negative during the evolution, according to data from Table 2.

Currently, the patient is asymptomatic, without changes in the brain resonance, but with some memory impairment.

Discussion

In this paper, the case of a patient with late diagnosed BYS and with severe neurological injury associated with joint and cutaneous manifestations is presented. A positive serology for *B. burgdorferi* (*sensu stricto*) helped confirm the diagnosis. Positive epidemiological history, presence of cognitive impairment and neuropsychiatric symptoms, along with a good response to treatment with disappearance of antibodies anti-spirochetes, were equally relevant to the diagnosis.

In Brazil, this zoonosis may have a long latency period between initial infection and the onset of symptoms, as well as with relapsing episodes during its evolution. Generally, the joint condition of BYS emerges in large joints, especially the knees, and can evolve to simulate rheumatoid arthritis, as it was in this case.[5,6,8] In this country, whenever there is presence of oligoarthritis of large joints, an investigation of BYS is mandatory, and one should search both the epidemiological and clinical histories.

LIM-17 adopts as diagnostic criteria for BYS the presence of major (positive epidemiology, MS or systemic symptoms, and positive serology) and minor (a history of systemic episodes compatible with BYS, symptoms of chronic fatigue or cognitive dysfunction, autoimmune disorders and visualization of spirochetes in peripheral blood) parameters.[11] The patient visited risk

Table 1 – Evolutionary analysis of the cerebrospinal fluid (CSF).

CSF	Ref	Internal medicine ward	Internal medicine ward	Outpatient´s unit	Outpatient´s unit	Outpatient´s unit	Neurology ward
Date		Dec 13, 06	Dec 15, 06	Mar 19, 07	Apr 04, 07	July 13, 07	July 30, 07
Leukocytes (/mm^3)	0 - 5	960	160	65	81	190	18
Neutrophils		1	3	7	42	6	0
Lymphocytes		94	90	76	41	73	67
Monocytes		3	6	17	15	19	21
Glucose (mg/dL)	50 - 90	41	44	55	48	63	80
Proteins (mg/dL)	< 40	62	49	38	43	32	30
B. burgdorferi							
ELISA IgM		-	-	-	Negative	Negative	-
ELISA IgG		-	-	-	Negative	Negative	-

Ref, reference value.

Table 2 – Evolutive analysis of serology for *Borrelia burgdorferi*.

B. burgdorferi Serology	Ref	Outpatient´s unit	Outpatient´s unit	Neurology ward	Outpatient´s unit	Outpatient´s unit
Data		Apr 11, 07	Aug 11, 07	Aug 23, 07	Sept 26, 07	Nov 14, 07
ELISA IgM	1/100	Neg	1/100	Neg	Neg	Neg
ELISA IgG	1/400	1/800	Neg	Neg	Neg	Neg
WB IgM	[a]	1 b	2 b	2 b	Neg	Neg
WB IgG	[a]	3 b	3 b	Neg	Neg	Neg

Neg, negative; Ref, reference value.
[a]WB is considered positive with presence of at least 4 IgG bands, or at least 2 IgM bands; or at least 2 IgG bands *and* 1 IgM band simultaneously. Ceftriaxone was initiated on June 29, 2007.

areas, socialized with domestic animals and had episodes of tick bites. The BYS vectors often infest animals living close to man.[1,6] The fact that the patient denied recent tick bites is not surprising, as the contagion may have occurred months or years before the current symptoms.

The concomitant occurrence of meningoencephalitis and the involvement of the second cranial nerve, associated with the joint manifestation, is a relevant aspect. Shinjo et al.,[10] studied 30 patients with BYS neuroborreliosis, and found that 73.6% had recurrence episodes, 56.7% had concomitant neurologic complaints with arthritis, and meningoencephalitis was identified in 33.3% of cases.

The encephalomyelitis of human borreliosis may be confused with multiple sclerosis (EM).[12,13] In this report, the exuberance of the inflammatory symptoms, the multiplicity of systemic complaints, a positive serology for *B. burgdorferi* and the good response to antibiotics excluded this diagnostic option. Other causes of infectious and autoimmune encephalomyelitis were also excluded.

There is no mention about MS in our patient's history, but it should be noted that this initial injury, which arises at the point of inoculation of spirochetes, occurs in less than 50% of cases in Brazil.[6,8] Interestingly, other atypical cutaneous presentations have been reported, such as panniculitis, lymphocytoma and scleroderma-like plate.[6,8,11,14] There is no record of erythema nodosum associated with BYS, but there are reports of erythema nodosum in patients with LD.[15]

This paper confirms the existence of recurring outbreaks in BYS patients. This finding is highly relevant, since the current symptoms are not always associated with epidemiological and clinical data of the past. However, due to the severity of illness, a good response of the condition to the treatment with antibiotics in its early stages, and the possibility of preventing progression to chronicity, physicians of different specialties should be vigilant for suspected cases of Brazilian human borreliosis.

Conflicts of interest

The authors declare no conflicts of interest.

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