MULTIPLE SCLEROSIS AND POSITIVE LYME SEROLOGY

MARCO AURÉLIO LANA-PEIXOTO*

SUMMARY - As Lyme neuroborreliosis (LNB) may clinically mimic multiple sclerosis (MS) the presence of antibodies to Borrelia burgdorferi in serum of patients with a MS-like disease in non-endemic areas for Lyme disease may be troublesome. We report the case of a 45-year-old white female with the diagnosis of relapsing/remitting form of MS due to a 15-year history of optic neuritis and recurrent episodes of motor and sensation disturbance in the upper right limb and in both lower extremities associated with bladder dysfunction. A magnetic resonance imaging of the brain revealed multiple high intensity periventricular white matter lesions. The patient had been exposed to ticks but did not recall the presence of erythema migrans. ELISA for Lyme disease was positive in two different laboratories and the positive serology was confirmed by Western blotting. No convincing reponse followed treatment with ceftriaxone. Although it is clear that the patient had been infect by Borrelia burgdorferi the relationship of this spirochetal infection with the neurological disease could not be ascertained.

KEY WORDS: Lyme disease, Lyme neuroborreliosis, multiple sclerosis, positive serology.

Serologia positiva para doença de Lyme e esclerose múltipla

RESUMO - As manifestações neurológicas da doença de Lyme são extremamente variadas e podem ocorrer de forma episódica e focal, às vezes simulando o quadro clínico da esclerose múltipla (EM). A situação pode se tornar ainda mais confusa quando pacientes com diagnóstico de EM apresentam anticorpos séricos anti-Borrelia burgdorferi, em áreas não endêmicas para a doença de Lyme. Relatamos o caso de uma paciente de 45 anos de idade com o diagnóstico de EM devido a episódio de neurite óptica há 15 anos e desde então surtos de distúrbios motores e sensitivos no membro superior direito e nos membros inferiores, associados a disfunção esfinctérica. A reação de ELISA para doença de Lyme foi positiva em dois laboratórios diferentes e a positividade foi confirmada por Western blot. Tratamento com ceftriaxone não produziu mudança significativa do quadro clínico. Embora a paciente deva ter sido infectada pela espiroqueta, desenvolvendo então anticorpos séricos específicos, a relação entre esta infecção pela Borrelia burgdorferi e a sintomatologia neurológica, no presente caso, permanece não esclarecida.

PALAVRAS-CHAVE: doença de Lyme, neuroborreliose, esclerose múltipla, serologia positiva.

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of unknown etiology characterized by involvement of different areas of the central nervous system. The diagnosis of MS is one of exclusion and a number of conditions must be ruled out by some particular clinical features of the disease and appropriate laboratory means. Lyme disease is a spirochetal disease that frequently affects the nervous system months or years after the infection giving rise to a varied clinical picture named Lyme neuroborreliosis (LNB). As LNB may manifest with episodic focal neurological involvement it seems in some instances indistinguishable from MS on clinical grounds and therefore has to be included in its differential diagnosis. The differentiation of LNB from MS may be sometimes more confusing when one considers the possible presence of antibodies to Borrelia.
*burgdorferi*, Lyme disease's causative agent, in serum of patients with definite MS. In highly endemic areas, as in some regions of the United States and Europe, this finding may represent no serious problem for the differential diagnosis. However, in areas of low or even unknown prevalence of the illness, like Brazil, the presence of positive Lyme serology in patients with a multiple sclerosis-like disease can lead neurologists through a difficult path to define the diagnosis and make the necessary therapeutic decisions.

Herein we report on a patient with typical clinical features of MS who was found to have serum antibodies to *Borrelia burgdorferi*. To the best of our knowledge no previous case showing this association has been reported in this country.

**CASE REPORT**

MS, a 45-year-old white female was referred for neurologic evaluation because of episodic weakness of the lower limbs associated with back pain, sensation disturbance in both legs and urinary sphincter dysfunction. She had a history of optic neuritis with a good recovery 15 years ago. Since then she had been presenting intermittent bursts of motor and sensation symptoms in the upper and lower extremities. In 1987 she was subjected to a magnetic resonance imaging of the brain which revealed multiple high intensity gadolinium enhanced periventricular white matter lesions compatible with the diagnosis of MS. Although the patient used to spend week-ends and vacations in a rural property and had been frequently exposed and bitten by ticks she had never noticed the presence of erythema migrans or other skin lesions. She had no history of cardiovascular, arthritic or other systemic symptoms and except for the visual impairment cranial nerve dysfunction had not been observed. Family history was of interest in that the patient's mother had had in her twenties an episode of paraparesis of unknown etiology followed by full recovery within a few weeks. On neurologic examination the best corrected visual acuity was 20/30 on each eye. There patient could read with each eye five out of eight plates of the Ishihara's color vision test. Fundi examination disclosed bilateral moderate optic disc atrophy. The pupils measured 3/3 mm in diameter and reacted fully to light and near stimuli. There was no pupillary afferent defect. Light touch and pinprick sensation were decreased on the right side of the face and on the right upper and lower extremities. Vibration sense was decreased on the right elbow and wrist and both lower limbs. Motor examination showed spastic paraparesis with brisk tendon reflexes and the presence of Babinski sign bilaterally. The patient could barely walk without assistance and on the Romberg maneuver she presented striking unbalance. Coordination tests revealed bilateral dysmetria, more striking on the right arm. Laboratory work-up including RBC, WBC, ESR, reactive C protein, antinuclear antibody, serum protein electrophoresis, blood chemistry and calcium, serum angiotensin-converting enzyme, serum VDRL and FTA-ABS, urinalysis, determination of 24-hour urinary calcium and chest X-rays failed to reveal any abnormality.

Serum ELISA test for *Borrelia burgdorferi*, showed IgG value of 73.1 (normal, <40) but IgM was negative. A repeat serology in another laboratory confirmed the results. Lyme Western blot was also positive. A new magnetic resonance imaging of the brain disclosed scattered high intensity gadolinium enhanced lesions in the white matter of the centrum semiovale and in the periventricular areas of both cerebral hemispheres. Spinal tap revealed opening pressure of 160 mm water and cerebrospinal fluid (CSF) analysis showed 8 lymphocytes/mm³, 31 mg/dL protein, 60 mg/dL glucose and nonreactive VDRL. CSF protein electrophoresis was normal. The patient was given by an outside physician intramuscular ceftriaxone sodium (1 g a day) for 42 days. When she came back for neurologic re-evaluation, one month after starting medication, she informed she was feeling better and that the back pain had disappeared. On examination she could walk a little better without assistance but still had moderate dysequilibrium. Sensation over the face was entirely normal, but the neurologic examination otherwise remained unchanged.

**COMMENTS**

Lyme disease is a tick-borne multisystem disorder caused by the spirochete *Borrelia burgdorferi*. It was described as a separate entity by Steere et al. in 1977 because of a clustering of children and adults in Lyme, Connecticut, presenting with oligoarticular arthritis and thought to have rheumatoid arthritis. The spirochete is transmitted by some Ixodes ticks, mainly found in the United States and European countries, although they have a worldwide distribution. As the tick is small only 30 percent of patients with Lyme borreliosis recall having had a tick bite. The infectious
agent of Lyme disease, *Borrelia burgdorferi*, has been recently isolated from blood, synovial and spinal fluid\textsuperscript{32}, and also identified in the retina, cornea and the vitreous of the eye as well as brain, skin, and other organs\textsuperscript{31}.

The clinical manifestations of Lyme borreliosis have been divided into three chronological stages although not all patients exhibit each stage. The symptoms and signs in each stage may be exceptionally varied making the recognition of the disease extremely difficult. The only pathognomonic criterion for diagnosing Lyme disease is the rash known as *erythema migrans* which was first described by Afzelius in Sweden, in 1909\textsuperscript{2}. It is a circular patch of spreading erythema starting at the site of the tick bite to become sometimes quite large. Some central clearing often occurs to give the ring-like lesion a “bull’s eye appearance”.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Manifestations</th>
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<tr>
<td>Stage one</td>
<td>Headache, meningismus</td>
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<tr>
<td>Stage two</td>
<td>Asseptic meningitis, Facial palsy, Diplopia, Optic neuritis, Anterior ischemic optic neuropathy, Neuroretinitis, Horner's syndrome, Bilateral tonic pupils, Argyll Robertson-like pupils, Blepharospasm, Other cranial neuritis, Pseudotumor cerebri, Mononeuritis multiplex, Polyneuritis, plexopathies, Painful radiculitis, Myelitis, Cerebellar ataxia, Chorea, Behavior disorders</td>
</tr>
<tr>
<td>Stage three</td>
<td>Chronic encephalomyelitis, Spastic paraparesis, Leukoencephalitis, Multiple sclerosis-like syndrome, Chronic fatigue syndrome, Chronic polyneuropathies, Dementia, Psychiatric disorders</td>
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The first stage of Lyme disease begins with erythema migrans and symptoms mimicking a flu-like illness as the spirochete disseminates throughout the blood stream. Fever, conjunctivitis, pharyngitis, lymphadenopathy, pneumonitis with dry cough and pleuritic pain and hepatosplenic tenderness may occur. Headaches and meningeal signs are frequently found at this stage. Erythema migrans lesions usually fade within a few weeks but may last longer and even recur in a later stage of the illness.

The second stage of the illness begins weeks to several months following inoculation and usually manifest by cardiovascular or neurological involvement. Ophthalmologic signs due to corneal, uveal, vitreous and retinal involvement may occur in late secondary or early tertiary disease\textsuperscript{31}. The neurologic spectrum of the disease is extremely wide at this stage although the triad of aseptic meningitis, cranial polynuereitis and painful radiculitis has been emphasized in stage two disease\textsuperscript{25}. Involvement of the central nervous system includes hemiparesis, spastic paraparesis, ataxia, gait disturbances, bulbar signs, seizures and dementia. Peripheral nervous system abnormalities are also well recognized\textsuperscript{11}. In about 15 percent of patients with Lyme disease a symptomatic meningitis will occur an average one month after infection. In addition to that patients with meningitis commonly present nausea, vomiting, malaise, fatigue and irritability. The most common cranial neuropathy is a facial palsy but the third, sixth and eighth nerves may also be involved. Optic neuritis in the form of papillitis or retrobulbar neuritis, neuroretinitis, papilledema and optic atrophy have been all described\textsuperscript{31}.

The third stage of Lyme disease is usually characterized by arthritis. Synovitis, vasculitis,
myositis, fascitis, peripheral neuropathies, acrodermatitis chronica atrophicans, lymphocytoma cutis, linear scleroderma, ulnar fibrous nodules and lichen sclerosus are also observed at this phase.

Tertiary LNB has been classified into: (1) progressive encephalomyelopathies which can be predominantly spinal or cerebral; (2) peripheral neuropathy; and (3) latent neuroborreliosis. At this phase symptoms and signs of a chronic encephalomyelopathy sometimes simulating MS can be observed. The clinical picture of chronic fatigue syndrome and a wide range of mental disturbances have been also reported. Magnetic resonance imaging of the brain may disclose multiple demyelinating white matter lesions similar to those found in MS. Because of the expanding spectrum of clinical manifestations Lyme disease has now emerged as the "great imitator" replacing syphilis and systemic lupus erythematosus. The most frequent manifestations of LNB are listed in Table 1.

As a rule the diagnosis of LNB is not straightforward as patients may not recall tick bites and erythema migrans can frequently not be present or can antedate neurological involvement by months or years. In addition to that systemic manifestations of the illness may be protean or very subtle. Diagnostic criteria for LNB have been proposed including categories for definite, probable and possible disease as shown in Table 2. The diagnosis of LNB currently rests on the association of a compatible picture with positive serology and an inflammatory CSF profile without other apparent explanation. Typically CSF analysis shows a lymphocytic pleocytosis and the presence of antibody to the organism, but these can be absent.

In the absence of erythema migrans the diagnosis of Lyme disease rests on the presence of positive serology as isolation of the spirochete from the blood, CSF or tissue samples depends upon special culture media and sophisticated techniques. Even under optimal conditions, the frequency of isolating Borrelia burgdorferi from the blood of acutely ill patients is less than 10 percent. Serology therefore plays an important role in the diagnosis of Lyme disease although the current available methods are still far from conclusive. Concern over the sensitivity, specificity, lack of standardization and interlaboratory variability of the tests has been raised by some authors who emphasize that the results of serology testing should not be relied on as the sole criteria in making the diagnosis of Lyme disease.

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**Table 2. Diagnostic criteria for Lyme neuroborreliosis (LNB)*.**

<table>
<thead>
<tr>
<th>Diagnostic categories</th>
<th>Description</th>
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<tr>
<td>I - Definite LNB</td>
<td>Neurological disorder with positive culture for <em>Borrelia burgdorferi</em></td>
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<tr>
<td>II - Probable LNB</td>
<td>A. Characteristic erythema chronicum migrans (ECM) followed by neurological disease, without other causes for neurological symptoms, or</td>
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<td>B. No ECM but a neurological disorder with all of the following items:</td>
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<td></td>
<td>a. Positive serology confirmed by Western blot</td>
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<td></td>
<td>b. Lymphocytic response in the CSF</td>
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<td></td>
<td>c. Sustained response to intravenous antibiotics</td>
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<tr>
<td></td>
<td>d. Absence of other clear diagnosis</td>
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<tr>
<td>III - Possible LNB</td>
<td>Neurological symptoms with positive serology with or without Western blot confirmation and lack of fulliment of items IIB “a”, “c” and “d” above</td>
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* Modified from Pachner and Delaney.
Indirect fluorescent-antibody test (IFA) and enzyme-linked immunosorbent assay (ELISA) have been the most used serological assays in clinical practice, the ELISA being favored because of the higher levels of sensitivity and specificity. False-negative results primarily occur during the early stages of the disease whereas false-positive serologic results, particularly with IgM, may be seen both in healthy individuals and in patients with a variety of diseases including syphilis, autoimmune and other neurologic disorders. Western blotting has been now widely used as a confirmatory diagnostic test when ELISA is positive. However it is more labor intensive and the criteria for positivity have not been established yet. Recently polymerase chain reaction (PCR) analysis of CSF was introduced providing a rate of false-positivity of less than three percent. On the other hand, PCR results have been found false-negative or indeterminate in more than one-half of definitive or probable cases indicating a very low level of the spirochete or spirochetal DNA in the CSF of a significant percentage of patients with LNB.

As the significance of positive Lyme serology in patients with clinical picture of MS is concerned, the definite diagnosis is particularly important as Lyme disease patients are to be given antibiotics. Coyle found that only one of 89 definite MS patients had serum antibodies to Borrelia burgdorferi in an highly endemic area, concluding that this infection is rare in MS patients. This finding is consistent with the work of Schmutzhard et al. who found low significant benefit from antibiotic treatment. More recently Coyle et al. examined the presence of antibodies to Borrelia burgdorferi in 283 MS patients in a highly endemic region for Lyme disease. They found that seven percent of the patients had a borderline or positive serology and only one patient had a truly suggestive history for Lyme disease. In eight patients a repeat serology was nonconfirmatory. Only in five out of 10 seropositive patients whose CSF was examined anti-Borrelia burgdorferi antibodies were found but none of them had evidence of intrathecal production of specific antibodies. Although patients were given a course of antibiotic treatment, no convincing neurological response was noted. The authors conclude that the incidental finding of positive Lyme serology in patients residing in a highly endemic region is unlikely to reflect LNB.

Our patient had history of frequent exposure to ticks but did not recall the presence of erythema migrans. She also had no symptoms of disease outside the nervous system. The first episode of neurologic involvement took place 15 years ago when she developed optic neuritis which converted to full multiple sclerosis later on. A wide variety of conditions mimicking MS were ruled out by laboratory work-up. Western blotting confirmed Lyme positive serology as shown by ELISA test performed in two different laboratories. However, CSF was not analysed for the presence of antibodies to Borrelia burgdorferi.

As the prevalence of Lyme disease in Brazil is largely unknown and to our knowledge only one case of LNB has been so far reported, the significance of positive serology to Borrelia burgdorferi in our MS patient could not be ascertained. It seems most likely that the patient had been infected by the spirochete developing serum specific antibodies. However, the relationship of the neurological disease with this antecedent spirochetal infection remains unclear.

REFERENCES