Uveitis associated with Lyme disease in Mexico

Uveítis secundaria a Borreliosis de Lyme en México

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Abstract

Objective: Lyme disease is a rare multi-systemic infection and like in many other countries, in Mexico it is rarely considered in the differential diagnosis of certain forms of uveitis due to lack of knowledge about the risk factors of *Borrelia burgdorferi* infection. This report aims to review such risk factors, the clinical characteristics of ocular involvement, as well as the keys to suspect the disease in susceptible patients. **Observations:** A 4-year-old female with a 6-week history of bilateral red eye and blurred vision. The patient referred muscular and joints pain, skin rash, and respiratory symptoms 10 weeks before. She was previously treated for bilateral panuveitis with topical and systemic steroids during 20 days without improvement. Visual acuity was 20/200, with 3+ cells in the anterior chamber, and 2+ diffuse vitritis. Blurred right disk margins, perivascular sheathing, and multiple chorioretinal white-cream-colored infiltrates in the peripheral retina of both eyes. Multifocal chorioretinitis, papillitis, and vasculitis were diagnosed with a positive serology for *B. burgdorferi*. Treatment consisted in 250 mg of oral amoxicillin every 8 h for 3 weeks, with complete resolution of inflammation. **Conclusions:** The diagnosis of Lyme disease at early stages is difficult due to its unspecific signs and inconsistent serology. Uveitis due to *B. burgdorferi* must be considered in every patient at risk who presents with neuro-ophthalmologic manifestations associated with chronic bilateral uveitis refractory to steroid therapy.

Key words: Ocular borreliosis. Lyme. *Borrelia burgdorferi*. Uveitis. Chorioretinitis. Neuroretinitis.

Resumen

Objetivo: La borreliosis de Lyme es una infección multisistémica rara, y al igual que ocurre en otros países, en México rara vez se considera en el diagnóstico diferencial de ciertas formas de uveítis debido al desconocimiento de los factores de riesgo de contagio por *Borrelia burgdorferi*. El presente reporte tiene como objetivo revisar dichos factores de riesgo, las características clínicas de la afección ocular, así como su sospecha en pacientes susceptibles. **Observaciones:** Paciente femenina, 4 años, con ojo rojo y visión borrosa bilateral de 6 semanas de evolución. Mialgias-artralgias, erupción cutánea y cuadro respiratorio las 10 semanas previas. Tratada como panuveítis bilateral con esteroides tópicos y sistémicos por 20 días sin mejoría. Agudeza visual 20/200, células 3+ en cámara anterior y vitreítis difusa 2+ en ambos ojos. Pérdida de bordes del nervio óptico derecho; exudados perivasculares e infiltrados coriorretinianos color blanco-cremoso en la periferia en ambos ojos. Se diagnosticó coriorretinitis multifocal, papilitis y vasculitis retiniana con serología positiva para *B. burgdorferi*. Tratada con amoxicilina 250 mg cada 8 h por vía oral por 3 semanas con resolución del cuadro inflamatorio. **Conclusiones:** El

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diagnóstico de borreliosis de Lyme en etapas tempranas es difícil debido a los signos inespecíficos y la seroconversión inconstante. La uveítis por *Borrelia burgdorferi* debe considerarse en todo paciente bajo riesgo que presente manifestaciones neurooftalmológicas asociadas a uveítis bilateral crónica refractaria a tratamiento con esteroides.

Palabras clave: Borreliosis ocular. Lyme. *Borrelia burgdorferi*. Uveítis. Coriorretinitis. Papilitis.

Introduction

Lyme borreliosis is a multisystemic emerging infectious disease caused by the spirochete *Borrelia burgdorferi*, which is transmitted by the bite from ticks of the genus *Ixodes*, the vector of the disease¹. *Ixodes scapularis*, the most frequent vector in the USA and present in the state of Texas, has also been found in areas of Coahuila². In addition, *Ixodes* have been identified in Baja California, the Yucatan Peninsula, the Gulf of Mexico and the northeastern area of the Mexican Republic³⁻⁵. The risk of infection is directly related to the prevalence of infected ticks and reservoirs, as well as exposure to endemic areas⁶.

In Mexico, the first cases of chronic migratory erythema associated with Lyme borreliosis were reported in Sinaloa and Monterrey in 1991^{7,8}. Eight years later, Gordillo, et al. reported a prevalence of *B. burgdorferi* infection of 1.1% in the general population of Mexico, meanwhile the prevalence of the white-tailed deer from the northeast of the country was of 3%⁴. The deer are the final hosts of adult *Ixodes*, and their primary function is to preserve the vector. Another study detected *Borrelia spp* in 16% of the resident dogs of the Monterrey metropolitan area¹⁰. By 2003, a seroprevalence of infection by *B. burgdorferi* of 3.4% in Mexico City and 6.3% in the general population of the northeast of the country, including the states of Nuevo León, Coahuila and Tamaulipas, had been reported. Tamaulipas had the highest seroprevalence⁵. In 2007, the first confirmed cases of skin and neurological disease from the Valley of Mexico and Quintana Roo¹¹ were reported.

One third of Lyme borreliosis cases occur in children under 18 years of age, and the age at greatest risk is between 5 and 14 years of age¹². In Mexico, since 1999, epidemiological surveillance has been maintained to identify cases of Lyme borreliosis in childhood¹³. Up to 2010, seventy-two children had been studied, with a mean age of 8.5 years, of which 55% presented cutaneous manifestations, 27%, neurological manifestations, and 18% arthritis. Almost 32% tested positive by immunoabsorbent enzyme assay (ELISA), and Lyme disease was confirmed in 28% of them by Western blot¹³. Seventy-five percent of these children had early

manifestations of the disease, which explains the low seropositivity index, while the remaining 25% showed late manifestations, but no ocular manifestations were identified in any of these cases¹³.

Lyme borreliosis can show several ophthalmological manifestations that are grouped into neuro-ophthalmic disorders, external ocular inflammation, intraocular inflammation, and retinal vascular disorders¹⁴. Lyme ocular borreliosis remains an underdiagnosed disease partly due to lack of awareness of its ophthalmologic manifestations and inclusion in the differential diagnosis of several ocular inflammatory disorders but also, due to the difficulty of obtaining a definitive serological diagnosis^{15,16}. In this report, we present the first case of uveitis secondary to Lyme borreliosis described in Mexico.

Case presentation

A 4-year-old female, resident from Monclova Coahuila, who was referred to the Immunology and Uveitis Service of our institution due to red eye, extreme photophobia, and bilateral blurred vision of 6 weeks of evolution. The patient belongs to a medium-low socioeconomic class, with a relevant history of previously living in the semi-rural area of the city of Longview in northeast Texas, a geographical area considered endemic for Lyme disease by the Center for Disease Control (CDC) from Atlanta, Georgia, USA, and also in the suburban area of Monclova, Coahuila, in northeastern Mexico.

The patient had been treated for bilateral panuveitis with topical and systemic steroids for 20 days without improvement, but with deterioration of her visual and inflammatory eye status. The indirect interrogation (parents) referred myalgia and arthralgia in the lower limbs and an upper respiratory tract infection manifested with fever, general malaise, rhinorrhea, and rash for 8 days. Such symptoms started 10 weeks before consultation. On physical examination, the patient had no obvious cutaneous, neurological or rheumatic manifestations associated with Lyme disease. Initial ocular examination revealed a best-corrected visual acuity of 20/200 with myopia (−1.25 diopters) and mild astigmatism (−0.50 diopters) in both eyes. External examination

showed ciliary injection 1+ and biomicroscopy demonstrated fine endothelial retrokeratic precipitates with a medial-inferior distribution and 3+ cells in the anterior chamber. The iris had no pathological alterations and the lens was clear. A diffuse vitritis of 2+ and subtle loss of the right optic nerve borders was observed by fundoscopy (Fig. 1), as well as peripheral segmental perivascular exudates of venular predominance and multiple round chorioretinal peripheral inflammatory infiltrates of approximately 50 μm in diameter, with a creamy white appearance (Fig. 2). Multifocal chorioretinitis, papillitis, and bilateral retinal vasculitis were diagnosed. In the initial approach, the following differential diagnoses were considered: juvenile idiopathic arthritis, systemic lupus erythematosus, infectious etiologies, such as syphilis, tuberculosis, atypical multifocal toxoplasmosis, bartonellosis and Lyme borreliosis. The following studies were requested: complete blood cell count, blood chemistry, C-reactive protein, erythrocyte sedimentation rate, urine analysis, antinuclear antibodies, serological determination of C3, C4, and CH50 complement fractions, tuberculin skin test (PPD), determination of fluorinated antibodies against *Treponema pallidum* (FTA-Abs), VDRL, IgG, and IgM antibodies against *Toxoplasma gondii*, *Bartonella henselae*, and *B. burgdorferi* (ELISA). The results of the serological tests were negative, except for the differential serological analysis ("2-tiered") for Lyme borreliosis, which tested positive for IgM antibodies (result: 1.21; reference: positive > 1.09) and IgG (result: 1.35; reference: positive > 1.09) by ELISA, and confirmed by Western-immunoblot. The latter was positive for the p41Kd IgM (flagellin), p23Kd IgM (Osp C), and p41Kd IgG bands, specific for *B. burgdorferi* (LabCorp Laboratory Corporation of America, Burlington, NC. USA.; endorsed by the CDC of Atlanta, GA.)

Based on the history of living in a suburban area of Coahuila, the travel and stay in a semi-rural area in northeast Texas, the presence of an acute respiratory condition with general malaise, myalgia, arthralgia, fever, and skin rash for more than one week, in addition to the absence of response to previous topical and systemic steroids, and due to the fundus findings and serological confirmation of *B. burgdorferi*, a diagnosis of uveitis secondary to Lyme borreliosis was made. Topical treatment was started with 0.1% fluorometholone acetate every 4 h and amoxicillin 250 mg every 8 h (weight-based dose: 50 mg/kg/day) orally for three weeks.

At the end of the treatment, absence of inflammatory cells in the anterior chamber and vitreous cavity was observed; the optic nerve borders were well-defined

Figure 1. Right optic nerve with blurred borders, slight hyperemia and vascular congestion.

Figure 2. Multifocal white-creamy deep chorioretinal lesions, in the infero-temporal quadrant of the right eye.

(Figs. 3 A and 3 B); there was absence of retinal vasculitis and in the peripheral retina the chorioretinal lesions were atrophic with a "punched-out" appearance (Figs. 4 A and 4 B). Best-corrected visual acuity was 20/50 in the right eye and 20/40 in the left eye. At her last follow-up visit, 4 months after treatment, the patient was asymptomatic, with no data of intraocular inflammation and with a preserved visual acuity. A new differentiated serology for Lyme borreliosis yielded negative results for antibodies by ELISA and absence of specific bands for *B. burgdorferi* by Western-immunoblot. The patient attended consultation 2 years later for

Figure 3. Right (A) and left (B) optic nerves, with well-defined borders and without vascular congestion.

Figure 4. Peripheral retina of the right eye (A) and left eye (B) showing multiple chorioretinal atrophic lesions with a diffuse distribution, as well as a clear vitreous.

myopia and astigmatism examination; she was asymptomatic and without any sign of active uveitis.

Discussion

Lyme borreliosis is the most common vector-borne disease in the US and some European countries^{17,18}. Despite being up to 6 to 12 times less reported than estimated, approximately 30,000 cases are reported to the CDC every year^{18,19}. The epidemiological context is very important for the early diagnosis of Lyme disease. Tick bites occur most likely in people who spend time in wooded habitats or with shrubs, and grasslands of endemic areas, especially between the months of May and November¹⁹. In this case, the history of having lived in an endemic area of northeastern Texas, in the US²⁰, and of living in the northeast area of Mexico, where the greatest seroprevalence of *B. burgdorferi* infection has been reported⁵, as well as being the one with the highest presence of *Ixodes scapularis*^{2,21} and its natural host, the white-tailed deer⁴, prompted the consideration of Lyme borreliosis in the differential diagnosis.

The clinical manifestations of Lyme disease have been divided into three stages: localized, disseminated and persistent¹. The first two stages are part of the early infection with *B. burgdorferi*, while persistent disease is considered a late infection²². Table 1 shows the main multisystemic and ophthalmological manifestations, as well as the duration and diagnostic methodology used in the different stages of the disease.

It has been estimated that ocular manifestations occur in only 1% of cases and may occur in any of the three stages of the disease^{14,22}. During the first stage, characterized by the appearance of erythema, migrans and an undifferentiated febrile condition, conjunctivitis, red eye, photophobia, and tearing can be observed^{23,24}. Conjunctivitis is the most common manifestation, reported in up to 11% of cases and occurring almost always in the first weeks of infection²³. In the second stage, dominated by neurological, and musculoskeletal symptoms, diplopia, facial palsy, internuclear ophthalmoplegia, blurred vision, and eye pain can be observed, as well as keratitis, episcleritis, anterior uveitis, multifocal chorioretinitis, papillitis, panophthalmitis, retinal venous obstructions, exudative retinal detachment, and orbital myositis^{14,24,25}. In the third stage, characterized by rheumatologic (arthritis), and neurological symptoms, all the ocular manifestations described in the second stage usually occur, but especially the most severe, such as intraocular inflammation^{12,16,24,26}. Intermediate uveitis is the most common form, but multifocal chorioretinitis is also observed as in this case, with retinal vasculitis¹⁴. It has not been established whether late-stage patients represent a failure to antibiotic treatment, or persistence of *Borrelia*, a new infection with another tick-borne pathogen or perhaps an autoimmune phenomenon²⁶.

In this report, everything suggests that the patient was in the second stage due to the time elapsed from the respiratory and unspecific febrile symptoms until the onset of ocular symptoms. Apart from the positive serological results and the type of ocular manifestations like multifocal chorioretinitis, retinal vasculitis, and papillitis, which are clinical manifestations consistent with this stage, the patient did not show rheumatic or neurological symptoms.

Erythema migrans is the clinical indicator of Lyme borreliosis; however, in 20% of cases, no rash is observed²⁷. In endemic areas, patients with erythema migrans and recent exposure to tick bites do not require serological studies for diagnosis^{19,27}. In these early stages of the disease, the possibility of false negative serological results is high and when these tests are positive, they fail to distinguish between an active or

Table 1. Systemic and ocular clinical features at different stages of Lyme borreliosis

Stage	Multisystemic manifestations	Ophthalmological manifestations	Time of onset and diagnostic method
First: Early localized	Erythema migrans (66% of cases), starts 7 days post-bite and persists for 2-3 weeks. Undifferentiated febrile illness (50% of cases), starts 1-7 days post-bite. Fever, chills, malaise, fatigue, myalgia, arthralgia, and headache.	Conjunctivitis, red eye, photophobia, and tearing.	Begins 1-30 days post infection. Clinical diagnosis. Serological tests are not recommended (due to false negatives).
Second: Early disseminated	Neurological (5-20% of cases), facial palsy, more common, meningitis and radiculopathy (Lyme triad), as well as encephalopathy, and musculoskeletal : migratory polyarthritis that evolves into a monoarticular process (knee, ankle, and wrist).	Diplopia, internuclear ophthalmoplegia, facial palsy, papilledema, blurred vision, pain, keratitis, episcleritis, and scleritis, uveitis (multifocal chorioretinitis), papillitis, panophthalmitis.	Arthritis starts from 3-10 weeks and meningitis from 2-10 weeks post infection. IgM and IgG antibodies against <i>B. Burgdorferi</i> (ELISA), confirmed by Western blot. PCR (limited availability)
Third: Late persistent or chronic	Rheumatic : knee arthritis (90% cases), and neurological : subacute encephalopathy, progressive chronic encephalomyelitis, axonal neuropathy, and myelitis (50% cases). Acrodermatitis chronica atrophicans on the back of the hands, feet, knees, and elbows (European).	Anterior, intermediate, or posterior uveitis, panuveitis, retinal vasculitis, orbital myositis, exudative retinal detachment, central, and branch vein occlusions.	Begins months to years after initial infection. IgG antibodies against <i>B. Burgdorferi</i> (ELISA), confirmed by Western blot. PCR (limited availability)

ELISA: immuno-absorbent enzyme assay; PCR: polymerase chain reaction.

past infection²⁸. In the same regard, the sensitivity of the differentiated serological analysis ("2-tiered") to detect IgM and IgG antibodies against *B. burgdorferi* in the serum of patients when the humoral immune response is developing, is of only 30-40%^{28,29}. Therefore, the diagnosis of Lyme ocular borreliosis in early stages of the disease is difficult, since it is based on nonspecific clinical findings related to ocular surface inflammation, intraocular inflammation or neuro-ophthalmic alterations in patients with a high risk of infection³⁰. For disseminated Lyme disease, the sensitivity of serological tests increases to 70-100%, while the specificity is high (95%) during all stages of the disease¹⁵. Other diagnostic tests are direct tests, specifically culture and polymerase chain reaction (PCR). Culture is not available for routine use; it is technically difficult to perform and is characterized by low diagnostic sensitivity. On the other hand, PCR is only performed in the synovial fluid of patients with arthritis and a suspected diagnosis of the disease, and there are isolated reports of its diagnostic utility in ocular tissues, such as conjunctiva, aqueous or vitreous humor^{31,32}. Thus, the diagnosis of uveitis secondary to Lyme borreliosis is based on the history of exposure to tick bites or hazardous environments; on a positive differential serological analysis during the disseminated and persistent stages; on the resistance to steroid treatment, and on the favorable response to antibiotic therapy, as well as on the

exclusion of other potential diagnoses^{33,34}. In this case, the patient had an epidemiological history considered as a risk for developing Lyme borreliosis, did not show improvement with steroid treatment and the serology for other causes of uveitis was negative. In addition, she had a frankly positive and confirmatory result of infection with *B. burgdorferi* by differentiated serology. In this regard, the patient was positive for p23Kd and p41Kd IgM bands and p41Kd IgG bands against *B. burgdorferi* by protein electrophoresis, which are typical in Lyme disease and that became negative after the fourth month of treatment^{27,29}. During the clinical course of Lyme borreliosis, seroconversion by ELISA and Western blot is observed, changing from positive to negative and vice versa, without following a regular pattern³⁵.

The differential diagnosis of Lyme ocular borreliosis should include any of the potential causes of the neuro-ophthalmic and inflammatory ocular manifestations observed in these cases, including viral conjunctivitis, herpes simplex virus, and varicella zoster infections, Rocky Mountain fever, Horner syndrome, sarcoidosis, facial, and trochlear paralysis, optic neuritis, sarcoidosis, syphilis, among others^{22,24,36}.

In terms of management, the conjunctivitis observed at the first stage of the disease usually does not require treatment, as is the case for the facial palsy observed in the second stage, which is usually self-limited, but

complications from exposure keratitis require supportive therapy. Episcleritis and keratitis are usually treated with a short course of topical steroids²⁵. On the other hand, in the case of neuro-ophthalmic disease with optic nerve involvement or intermediate uveitis, posterior uveitis, and panuveitis, the use of systemic steroids should be accompanied by antibiotic therapy. Usually the treatment consists of 2 to 3 weeks of penicillin-G, doxycycline, cefuroxime, cefotaxime, or ceftriaxone²⁶. In childhood, the first-choice oral antibiotic is amoxicillin (50 mg/kg/day up to a maximum dose of 500 mg/day), which is why in this case we decided to use it, although penicillin V sodium, and ceftriaxone may also be used³⁷. A systematic review of antibiotic therapy in children with Lyme borreliosis found no difference in therapeutic efficacy between different antibiotics³⁷. Recurrences of Lyme borreliosis, especially third-stage arthritis, are treated with steroids²⁶.

Our patient was a 4-year-old in the second stage of the disease, and had received systemic steroids for 3 weeks without response. For these reasons it was decided to suspend them. In conclusion, uveitis secondary to Lyme borreliosis is a rare entity probably underdiagnosed in our country. The limited epidemiological information and the lack of serological scrutiny in patients with suspected disease, contribute to the low diagnosis. When any bilateral panuveitis is under study, an exhaustive interrogation must be performed, including history about the way and place of living (geographical area), especially of high-risk habitats for *B. burgdorferi* infection. In our country, such history should be considered, especially in patients from the northeast area and its border with the state of Texas, USA. In any suspected or at-risk patient with neuro-ophthalmic manifestations associated with bilateral uveitis and in whom other infectious and frequent immune processes that do not respond to steroids have been ruled out, Lyme borreliosis should be considered as a differential diagnosis.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

None to report.

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