SEROLOGICAL EVIDENCE OF *Borrelia burgdorferi* INFECTION IN MEXICAN PATIENTS WITH FACIAL PALSY

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**ABSTRACT**

**Background:** Facial palsy is the most frequent manifestation of neuroborreliosis in the United States, Europe, and Asia, whereas in Mexico, its frequency is unknown. **Objective:** We aimed to determine the frequency of *Borrelia* spp. infection in patients with acute facial palsy in Mexico. **Materials and Methods:** In this cross-sectional, referral hospital-based survey, 191 patients with facial palsy were selected and clinical and epidemiologic data recorded. IgM and IgG serum antibodies to *Borrelia burgdorferi* were tested by enzyme-linked immunosorbent assay (ELISA) and confirmed by Western-Blot (WB). IgM and IgG antibodies against the herpes viruses HSV-1, HSV-2, cytomegalovirus, and Epstein-Barr virus were tested by ELISA. **Results:** 71 patients (37%) tested positive by ELISA to either *Borrelia* spp. or the herpes viruses. Of 25 patients (13%) who tested positive for *B. burgdorferi* by ELISA, 23 (12%) were confirmed by WB; 14 had IgM and 9 had IgG antibodies. Among the 14 IgM-WB positive patients, two cases recognized antigens of *B. burgdorferi* sensu stricto (s.s.), 10 of *Borrelia garinii* and 2 of *B. afzelii*, whereas all 9 IgG-WB positive were reactive against *B. burgdorferi* s.s. 14 patients had facial palsy in addition to other clinical data compatible with Lyme borreliosis. Patients infected with *B. burgdorferi* s.s. had a longer recovery time and a significantly higher risk (odds ratio 4.4, 95% confidence interval 1.5-12.9) of recurrent facial palsy than patients infected with other *Borrelia* genospecies. **Conclusions:** *Borrelia* infection is frequent in facial palsy patients in Mexico, with *B. burgdorferi* s.s. and *B. garinii* being the most frequent causative species.

**Key words:** Facial palsy. *Borrelia burgdorferi*. Lyme borreliosis. Neuroborreliosis.

**INTRODUCTION**

Lyme borreliosis is classically caused by the spirochete *Borrelia burgdorferi* sensu lato (s.l.) and transmitted to humans by an infected tick bite (*Ixodes* spp). This disease is endemic in the United States, Europe, and in some Asian countries, and infection has spread from rural to urban zones. Its incidence in the United States increased over two-fold between 1991 and 2009 and has remained high, averaging around eight cases per 100,000 persons. *B. burgdorferi* sensu stricto (s.s.) is the predominant genospecies in the United States, whereas *Borrelia afzelii* and *Borrelia garinii* are more prevalent in Europe and Asia1-4. In Mexico, recent
reports have documented the presence of *B. burgdorferi* in the vector, the reservoir and in clinical cases, suggesting that Lyme disease is an emerging infection in our country\textsuperscript{5–10}.

Lyme borreliosis has a broad range of clinical manifestations, affecting the skin, joints, heart, and musculoskeletal and nervous systems. Neuroborreliosis, acute facial nerve palsy, and meningitis are the most common manifestations in the disseminated stage of the disease. The reported frequency of facial palsy in Lyme disease is 25–50\% in the United States and 65\% in Europe; moreover, facial palsy is the sole clinical manifestation in about 20\% of cases\textsuperscript{11–15}. The diagnosis of neuroborreliosis is complex since patients usually do not recall a tick bite or have previously noticed the diagnostic erythema migrans; the skin rash or neurological symptoms are nonspecific at presentation. The diagnosis of facial palsy secondary to Lyme borreliosis is even more difficult, and the etiology is generally suggested when serological studies are positive. Other infectious agents associated with facial palsy include the herpes viruses (Herpes simplex, Epstein-Barr virus [EBV], cytomegalovirus [CMV], and Varicella-Zoster) and to a lesser extent, other viruses such as adenovirus, HIV, influenza, rubella, and mumps virus\textsuperscript{15–17}. In this study, we aimed to elucidate whether *B. burgdorferi* infection was associated with cases of facial palsy in patients treated in a general hospital in Mexico City.

**MATERIALS AND METHODS**

**Patients and serum samples**

A total of 830 consecutive patients with facial palsy, regardless of sex or age, were recruited in a cross-sectional survey at the rehabilitation hospital, a referral general hospital of the Social Security Institute in Mexico City, between April and December 2012. We excluded patients whose disease course was ≥8 weeks (211), patients with diabetes (224), arterial hypertension (198), or neoplasia (6); we subsequently selected 191 patients with a clinical course lasting ≤8 weeks. The study was approved by the ethical review board of the Rehabilitation Hospital. Informed consent was obtained from all patients. A blood sample was drawn from each patient at inclusion, and in cases with a clinical course ≤4 weeks, a second sample was obtained 4 weeks later.

**Laboratory procedures**

Initial serodiagnosis for the detection of IgM and IgG antibodies against *B. burgdorferi* was performed using a commercial enzyme-linked immunosorbent assay (ELISA) (Enzygnost Borreliosis, Dade Behring, Marburg, Germany). Samples positive in the ELISA assay were tested by Western-Blot (WB), using whole-cell antigens from the three main species within the *B. burgdorferi* sensu lato complex, *B. burgdorferi* s.s., *B. afzelii*, and *B. garinii* (kindly supplied by Dr. B. Jaulhac, Strasbourg, France)\textsuperscript{18}. Samples were also tested using a commercial immunoblot assay for the detection of specific IgG antibodies against *B. burgdorferi* s.s. (MarDx Diagnostics, Carlsbad, CA). A case was defined as positive for *B. burgdorferi* s.s. if the IgM or IgG ELISA tests were positive and confirmed by a positive IgM-WB in which antibodies reacted with at least 2 of 3 protein bands (21–24, 39, and 41 kDa), or by a positive IgG-WB with antibodies against at least 5 of 10 protein bands (18, 21–24, 28, 30, 39, 41, 45, 58, 66, and 93 kDa). *B. garinii* infection was confirmed based on the EUCALB (the European Union Concerted Action on Lyme Borreliosis) criteria for WB, with positive IgG antibodies against protein p17, and against at least two other protein bands (p83/100, p58, p43, p39, p30, OspC, and p21). Similarly, *B. afzelii* infection was confirmed by WB with IgG antibodies against protein p14 and at least one additional protein (p83/100, p39, p30, OspC, or p21). Criteria for IgM-WB for *B. afzelii* are based on positive antibodies against at least one protein band (p39, OspC, p17, or p41), whereas *B. garinii* seropositivity requires antibodies against at least one protein band (p39, OspC, or p41)\textsuperscript{18–20}.

Sera were also tested for specific IgM and IgG antibodies against Herpes simplex virus I and II, EBV, and CMV using commercial assays (ELISA Gull Kit, CMV or Quorum kit, USA).

**Statistical analysis**

Statistical analysis was performed with the Epi Info 3.2 program for descriptive statistics. Clinical differences between infected and uninfected patients were determined using Student’s t-test, $\chi^2$, or Fisher’s exact test, and odds ratio (OR) with 95\% of confidence intervals (CI); $p < 0.05$ was considered statistically significant.
RESULTS

A total of 191 patients were included into the study, with a mean age of 45 ± 17 years; 89 were male (46.5%) and 102 were female (53.5%). The mean duration of the facial palsy episode was 23.8 days (95% CI 20-27.4). Unilateral facial palsy occurred in 188 cases (98.4%), and only 3 had bilateral palsy; in addition, 37 (19.3%) patients had recurrent episodes. Five patients (2.6%) referred a recent tick bite and 103 (53.9%) were exposed daily to potential tick carriers (dogs, cats, birds, and cows). Among the five patients who reported a recent tick bite, three patients developed Lyme borreliosis and two were negative for the disease.

Serodiagnosis

Seventy-one patients (37.1%) were positive for B. burgdorferi or herpes virus infection by ELISA: 46 (24%) were positive for IgM antibodies against the tested herpes viruses (HSV-1, HSV-2, CMV, and EBV), and 25 (13%) for B. burgdorferi. 23 of the 25 B. burgdorferi cases (12%) were confirmed by WB testing and were considered as true positives: 14 were positive for IgM and 9 for IgG antibodies (Table 1). Five of these 23 cases were negative in the first sample but seroconverted in the second sample, 3 cases for IgM and 2 for IgG. Among the 14 IgM-WB positive cases, two samples recognized antigens of B. burgdorferi s.s., 10 were positive for B. garinii, and two for B. afzelii. All 9 IgG-WB cases were reactive against B. burgdorferi s.s. antigens, with antibodies against the 41, 58, 45, 66, and 93 KDa proteins (Table 1).

Clinical characteristics

The 14 patients positive for IgM by WB had a shorter disease course (mean: 20 days, 95% CI 5.40-34.60) than those positive for IgG (mean 38 days, 95% CI 9.34-54.82) (p > 0.05). Furthermore, four patients with a short clinical course (median: 13 days) had IgM antibodies recognizing low molecular weight proteins (23 or 18 KDa), whereas nine patients with a longer course (median: 55 days) had IgG antibodies against high molecular weight proteins (93 or 66 KDa).

In 10 of the 23 (44%) cases positive by WB, facial palsy was the only clinical manifestation, whereas the remaining 14 patients presented additional manifestations (Table 2). Patients infected with B. burgdorferi had an increased risk of developing recurrent episodes of facial palsy than those not infected (OR = 4.4; 95% CI 1.5-12.9; p < 0.01). In samples obtained during recurrent facial palsy episodes, IgG antibodies against B. burgdorferi were identified in nine patients and IgM was found in two cases.

About 71% of patients infected with Borrelia spp. were evaluated during the summer-autumn seasons, while noninfected cases of facial palsy were more evenly distributed throughout the year. All patients positive for B. burgdorferi were permanent residents of Mexico City, mainly from the city’s central area. Only six patients had traveled in the 2 months prior to the symptoms development, to other areas of the country: Three patients had visited the Zacango zoo and La Marquesa park (state of Mexico), two had been at the Paricutín volcano park (state of Michoacán), and one had visited the state of Zacatecas. Patients infected with B. burgdorferi were treated with tetracycline for 14 days, and their mean time to recovery

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Table 1. Serology findings in 191 patients with facial palsy in Mexico City

<table>
<thead>
<tr>
<th>Infectious agent</th>
<th>Positive test ELISA</th>
<th>Positive test Western Blot</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. burgdorferi sensu stricto</td>
<td>IgM: 7, IgG: 6</td>
<td>IgM: 2, IgG: 9</td>
</tr>
<tr>
<td>B. garinii</td>
<td>IgM: 14, IgG: 3</td>
<td>IgM: 10, IgG: 0</td>
</tr>
<tr>
<td>B. afzelii</td>
<td>IgM: 4, IgG: 3</td>
<td>IgM: 2, IgG: 0</td>
</tr>
<tr>
<td>Herpes simplex 1</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Herpes simplex 2</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

*Six cases were positive for both IgG and IgM. ELISA: Enzyme-linked immunosorbent assay

Table 2. Additional clinical characteristics in facial palsy patients infected with B. burgdorferi

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>N=23 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent facial palsy</td>
<td>7 (30%)</td>
</tr>
<tr>
<td>Arthritis, arthralgia</td>
<td>5 (22%)</td>
</tr>
<tr>
<td>Atroventricular block</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Erythema migrans</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>None</td>
<td>9 (39.1)</td>
</tr>
</tbody>
</table>

B. burgdorferi: Borrelia burgdorferi
Recovery after antibiotic treatment in Borrelia-infected patients was 4 weeks shorter than in infections caused by other agents, suggesting that an opportune diagnosis and appropriate treatment could decrease the recovery period; however, these results require confirmation in larger studies.

Some study limitations include the fact that it was conducted in a tertiary care hospital, which favors delayed patient referral as well as selection bias since not all facial palsy cases are referred to these hospitals. Antibodies were determined in blood samples but not in cerebrospinal fluid because in Mexico, this invasive procedure is not indicated in cases of facial palsy, as it is in other countries. In regard to treatment, there is an important limitation because there is no consensus on when to begin antibiotic therapy, especially in cases with a prolonged clinical course.

In this study, all Borrelia-infected patients received antibiotic treatment and the time to facial palsy resolution was not established in infected cases that did not receive antibiotics. Therefore, a different study design is required to evaluate the benefit of antibiotics in this condition.

In conclusion, our study findings confirmed the presence of B. burgdorferi s.l. infection in about 12% of cases of facial palsy in Mexico City. The B. genospecies, B. afzelii, and B. garinii were detected in cases of disseminated neuroborreliosis suggesting an epidemiological pattern similar to that found in Europe rather than to the pattern found in the United States.

**ACKNOWLEDGMENTS**

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**REFERENCES**