Lyme Borreliosis and Facial Paralysis–A Prospective Analysis of Risk Factors and Outcome

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Purpose: To evaluate the incidence of Lyme borreliosis in patients with acute idiopathic facial paralysis with special emphasis on the risk factors that explain the poor outcome of facial paralysis and occurrence of Lyme borreliosis.

Materials and Methods: During a 2-year period, we prospectively studied 503 consecutive patients with acute idiopathic facial paralysis for the presence of Lyme borreliosis. We screened the patients for antibodies to Borrelia burgdorferi and for symptoms or signs related to Lyme borreliosis. Chi-square and logistic regression tests were used for the statistical analysis. Special attention was paid to strict criteria for the diagnosis of Lyme borreliosis.

Results: Eleven (2.2%) of the 503 patients with facial paralysis had Lyme borreliosis. Fever, headache, pharyngalgia, enlarged cervical lymph nodes, bilateral paralysis, and arthralgia were more common in patients with Lyme borreliosis than in those without it. In the logistic regression modeling the best combination of explanatory variables for predicting the occurrence of Lyme borreliosis included summer season at the onset of facial paralysis, presence of enlarged cervical lymph nodes, and arthralgia. The best combination of explanatory variables to predict the poor outcome of facial paralysis was total paralysis of facial nerves, recurrent facial paralysis, and hyperacusis.

Conclusions: Lyme borreliosis is an important infectious cause of facial paralysis. In our study, 11 of 503 patients with acute idiopathic facial paralysis had Lyme borreliosis. The screening for serum antibodies in addition to the thorough evaluation of the history of the patient and of the patient’s clinical signs or symptoms possibly linked with Lyme borreliosis, are essential when diagnosing Lyme borreliosis.

it has been found in 6% to 20% of adult patients with FP. The incidence of LB is higher in children with FP than in adults with FP. In studies on pediatric FP, as many as two thirds of the patients have had LB. In a German multicenter study, LB was diagnosed in every third child with FP all year around and in every second child during the warm season. Thus, LB was the most frequently verifiable cause of FP in that study.

Bilateral occurrence is a special feature of the FP caused by LB. Paralysis is bilateral in 18% to 25% of the FP patients with LB, whereas the prevalence of bilateral paralysis is only 0.3% to 2% in Bell’s palsy.

In the current prospective study we screened consecutive patients with FP for antibodies to Borrelia burgdorferi and for symptoms or signs related to LB. We analyzed the risk factors for the occurrence of LB among the FP patients and for a poor outcome of FP. Strict criteria were applied for the diagnosis of LB.

PATIENTS AND METHODS

From 1 January, 1993, through 31 December, 1994, 503 consecutive patients, visiting the Department of Otolaryngology at the Helsinki University Central Hospital with acute idiopathic lower motoneuron FP, were enrolled in the study. The demographic data and clinical characteristics of the patients are presented in Table 1.

### Criteria for the Diagnosis of LB

In addition to positive levels of serum antibodies against B. burgdorferi, the diagnosis of definite LB was based on at least one of the following findings: 1) erythema migrans (EM) during recent weeks; 2) diagnostic levels of antibodies to B. burgdorferi in the cerebrospinal fluid (CSF); 3) a positive polymerase chain reaction (PCR) test for B. burgdorferi flagellin; 4) CSF pleocytosis in children; and 5) oligoarthritis. EM was defined as a red or bluish-red patch with an advancing edge that expanded over a period of days to weeks. An exception to the above-mentioned criteria was one seronegative patient who exhibited positive levels of antibodies to B. burgdorferi in the CSF.

Questionnaire I was given to all of the patients on admission. It was satisfactorily filled out by 279 of the 503 (55%) patients—the numbers in the different groups being 9 of 11 (82%) in the LB group and 270 of 492 (55%) in the non-LB group. After the mean follow-up of 45 months, all the patients received another questionnaire by mail (II). It was completed by 375 of 503 (75%) patients—the numbers in the different groups being 8 of 11 (73%) in the LB group and 367 of 492 (75%) in the non-LB group. Questionnaire I included questions about other diseases, pregnancy, other symptoms preceding (last few weeks) or coinciding with FP (including enlarged cervical lymph nodes), previous tick bites, skin lesions resembling EM, neuro-otological symptoms (including vertigo and hearing disorders), and symptoms or signs suggestive of LB (arthritis, arthralgia, myalgia, headache, fever of unknown origin, or fatigue). Questionnaire II included questions concerning recovery from FP and possible residual symptoms.

### Table 1. Clinical and Demographic Characteristics of the 503 Patients with Facial Paralysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With LB</th>
<th>Seropositive Patients</th>
<th>Seronegative Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n</td>
<td>11</td>
<td>50</td>
<td>442</td>
</tr>
<tr>
<td>Age, mean (range)</td>
<td>28.3 (1-61)</td>
<td>47.0 (3-92)</td>
<td>45.7 (1-86)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>4 (36)</td>
<td>26 (52)</td>
<td>218 (49)</td>
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<tr>
<td>Female, n (%)</td>
<td>7 (64)</td>
<td>24 (48)</td>
<td>224 (51)</td>
</tr>
<tr>
<td>Side of the paresis</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Right, n (%)</td>
<td>5 (46)</td>
<td>15 (30)</td>
<td>216/428 (51)†</td>
</tr>
<tr>
<td>Left, n (%)</td>
<td>4 (36)</td>
<td>35 (70)</td>
<td>202/428 (47)†</td>
</tr>
<tr>
<td>Bilateral, n (%)</td>
<td>2 (18)</td>
<td>0</td>
<td>10/428 (2)§</td>
</tr>
<tr>
<td>Total paresis, n (%)</td>
<td>5 (45)</td>
<td>12/44 (30)†</td>
<td>101/405 (25)‡</td>
</tr>
<tr>
<td>Tick bite, n (%)</td>
<td>6 (55)</td>
<td>10/49 (20)$</td>
<td>57/209 (27)</td>
</tr>
</tbody>
</table>

Abbreviation: LB, Lyme borreliosis.

*Data of 14 patients missing.
†Data of 6 patients missing.
‡Data of 37 patients missing.
§Data of 1 patient missing.
$Data of 233 patients missing.
Measurement of Immunoglobulin M and G Antibodies Against Borrelia burgdorferi

An enzyme-linked immunosorbent assay (ELISA) kit (Dako, Glostrup, Denmark) that uses B. burgdorferi flagellin as the antigen was used for the titration of antibodies in serum, as has been described previously. The cutoff titers for serum immunoglobulin IgG and IgM antibodies were 500 and 2,500, respectively. These cutoff titers conform with the antibody level 3 standard deviations above the mean of a reference population living in an area in central Finland with a low LB prevalence. The antibodies to B. burgdorferi in the CSF were tested by the same method used for serum. The cutoff limits for both the IgM and IgG antibodies in CSF were 3.0 in the same scale as applied to serum analysis. The IgG antibody titer of the CSF was divided by the total IgG concentration in the CSF. A corresponding ratio between the IgG antibodies and the total IgG concentration in the serum was also calculated. If the calculated ratio of the CSF was more than 2-fold higher than that of the serum, the IgG antibodies to B. burgdorferi in the CSF were considered to be intrathecally synthesized. Routine chemical and cytological analyses were performed on the CSF. Syphilis was ruled out as a source of false-positive serological results by an examination for Treponema pallidum antibodies (hemagglutination assay; Porton Cambridge, Newmarket, Great Britain).

Polymerase Chain Reaction

A 497-bp fragment of the gene encoding the 41-kd flagellin of B. burgdorferi sensu lato was amplified by PCR from samples of the the blood and CSF of the patients. To avoid contamination, the pre- and post-PCR procedures were carried out in separate laboratory rooms, and positive displacement pipettes were used in dispensing the reagents. Each PCR run included a positive control containing DNA extracted from a reference strain of B. burgdorferi (ATCC 35210). Furthermore, every fifth tube of each run was used as a negative control and subjected to all sample treatment procedures.

Statistical Analysis

The unpaired student t test, chi-square, and logistic regression test were used for statistical analyses with StatView 4.5 software (Abacus Concepts, Inc, Berkeley, CA) and S-Plus 4 software (MathSoft, Seattle, WA).

Ethical Considerations

The study protocol was approved by the Research Ethical Committee of the Department of Otorhinolaryngology in the Helsinki University Central Hospital.

RESULTS

Of the 503 FP patients, 11 (2.2%) had LB (LB group). The characteristics of the patients with LB are shown in Table 2. Three patients with LB had a recent history of untreated EM. The standard treatment of LB in this study included 2 g or 100 mg/kg (in children) of ceftriaxone once a day for 14 days. Median delay between onset of FP and the beginning of the ceftriaxone treatment was 13 days (range, 3-279 days). In addition to the course

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Serum Antibodies</th>
<th>CSF Antibodies</th>
<th>CSF Pleocytosis</th>
<th>CSF Protein</th>
<th>Serum PCR</th>
<th>CSF PCR</th>
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<td>7/f</td>
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</table>

Abbreviations: +, positive finding or result; -, negative finding or result; CSF, cerebrospinal fluid; EM, erythema migrans; Ig, immunoglobulin; PCR, polymerase chain reaction; m, male; f, female; ND, not done.

*Patient with oligoarthritis.
of ceftriaxone one patient received amoxicillin 1 g twice a day for 100 days.

The median interval between the onset of FP and the assessment of antibodies to *B. burgdorferi* was 4 days (range, 0-20 days). In the LB group the geometric mean levels of the serum IgM and IgG antibodies to *B. burgdorferi* were 2.3-fold and 3.2-fold higher than the cutoff limits, respectively. Three patients had IgG antibodies only, and 7 patients had both IgG and IgM antibodies. None of the patients had IgM antibodies only. The *T. pallidum* hemagglutination assay was done for 8 of the 11 cases, and it was negative in all of them.

CSF specimens from the 11 patients with LB were analyzed on admission, and 9 of them showed abnormalities. Eight (73%) were positive for antibodies to *B. burgdorferi*. Five patients had both IgM and IgG antibodies, 1 had IgM antibodies only (IgG antibodies not done), and 2 had IgG antibodies only. The geometric mean levels of the IgM and IgG antibodies were 46-fold (range, 3.3-530) and 24-fold (range, 2.3-330) higher than the cutoff limits, respectively. The *Borrelia* PCR test was carried out on CSF samples of 10 of the 11 patients and the sera of 9 of the 11 patients; the test was positive for one CSF sample only. Five (45%) of the patients had pleocytosis in the CSF (geometric mean of the leukocyte count, $148 \times 10^3/L$; range, 26-560 $\times 10^3/L$). An elevated protein concentration (mean, $2,780$ mg/L; range, 1,420-4,370 mg/L) was found in three patients.

In addition to the 11 patients with LB, 50 (10%) other patients with FP had positive levels of antibodies to *B. burgdorferi* in their sera (seropositive group). The median interval between the onset of the FP and the assessment of the antibodies in the seropositive group was 3 days (range, 1-32 days). Twenty-three (46%) of the patients had IgM antibodies only, 22 (44%) had IgG antibodies only, and 5 (10%) had antibodies of both classes. The geometric mean levels of the IgM and IgG antibodies were 1.5-fold (range, 1-11) and 1.7-fold (range, 1.4-2) higher than the cutoff limits, respectively.

A CSF specimen was obtained from 22 of these 50 patients in the seropositive group. Two patients had pleocytosis without any other abnormalities in their CSF. The *T. pallidum* hemagglutination assay was negative in all cases.

In addition to the 11 patients with LB, 2 patients in the seropositive group were also treated with intravenous ceftriaxone once a day for 14 days because of clinical suspicion of LB. Patients with idiopathic FP did not receive any medical treatment for their FP. Special emphasis was placed on the care of the eye.

With respect to the seasonal variation of FP, the time periods compared were the winter-spring season (December–May) and the summer-autumn season (June–November). FP occurred evenly throughout the year in the non-LB group, whereas all but one FP case in the definite LB group appeared during August–October. The incidence of FP in the LB group was highest in September (Fig 1). The seasonal distribution of FP in the LB group differed significantly from the distribution in the non-LB group ($P = .039$).

The occurrence of bilateral FP in the LB group and the seronegative group was 18.2% and 2.3% ($P = .0015$), respectively. None of the 50 patients in the seropositive group had bilateral paralysis.

The questionnaire data were cross-tabulated, and the significance of single symptoms and signs was evaluated as explanatory factors for LB and the outcome of FP. Fever during the last 3 weeks before FP was more common ($P = .0018$) in the LB group than in the non-LB group. This was also the case with headache ($P = .012$), pharyngalgia ($P = .015$), enlarged cervical lymph nodes ($P = .0062$) and arthralgia ($P = .036$). Swedish as a native language was more common in the LB and seropositive groups than in the seronegative group ($P = .026$).

The best model to explain the occurrence of LB included the following factors: presence of enlarged cervical lymph nodes, presence of arthralgia, and season at the time of FP (summer-autumn season compared with winter-spring season). The odds ratios (OR) for these factors were 10 [95% confidence interval (CI), 1.9-52], 7.0 (95% CI, 1.3-36) and 7.7 (95% CI, 0.84-70.8), respectively. These OR values corresponded to the maximum and minimum probabilities of $P = .436$ and $P = .00145$, respectively, for the patients having LB. The prospectively collected material allowed us to
calculate the probabilities based on the OR values. These calculations indicated that a patient suffering from FP during the warm season of the year with closely preceding or coinciding enlarged cervical lymph nodes and arthralgia, has a probability as high as 0.44 for LB. In contrast, a patient with FP during the winter, without enlarged cervical lymph nodes and arthralgia, is very unlikely to have LB ($P = 0.0014$).

In the final evaluation, recovery was considered incomplete even for some patients with minor complaints of facial motor function or eye symptoms, equaling that of House and Brackmann’s group I. A chi-square analysis indicated a worse outcome for the patients with total paralysis ($P = 0.002$), with previous FP ($P = 0.0005$), with arthralgia ($P = 0.005$), with vertigo ($P = 0.02$), and with nausea ($P = 0.01$). Female patients also had a worse outcome than male patients ($P = 0.01$). A trend ($P = 0.06$) for more common hyperacusis was observed in the patients with incomplete recovery.

There was no difference between the outcome of seronegative and seropositive groups ($P = 0.13$). Patients with LB, however, had more favorable outcomes than patients in seropositive ($P = 0.007$) or in seronegative ($P = 0.04$) groups.

Modeling with logistic regression was carried out to explain the FP outcome. The original explanatory variables selected were the type of FP (complete or partial paralysis), previous facial paralyses, gender, arthralgia, nausea, vertigo, and hyperacusis. The best model to explain the outcome of FP included type of FP, previous facial paralysis, and hyperacusis. The OR values for these factors were 2.7 (95% CI, 1.3-5.6), 7.0 (95% CI, 2.7-18) and 2.5 (95% CI, 1.0-6.3), respectively. The results indicate that a patient with partial FP for the first time without hyperacusis has a high probability ($P = 0.748$) to recover completely. On the other hand, a patient with recurrent and total FP and hyperacusis has a low probability ($P = 0.06$) of completely recovering.

**DISCUSSION**

We found out that 11 (2.2%) of the 503 patients with FP had LB. Our results are in accordance with the results of previous studies showing the relationship between FP and LB.$^9$-$^11,17,18$ The prevalence of positive levels of antibodies against *B. burgdorferi* in our FP patients exceeded remarkably their prevalence in the local population. According to our criteria for LB, 11 (18%) of the 61 seropositive patients had LB-related FP. The relationship between LB and FP among the remaining 50 seropositive patients remains speculative. A positive serological finding in a patient can be a sign of old immunity, or it can be based on a false-positive reaction. However, it seems likely that at least some of those
patients might have active LB. The relatively low antibody levels and evenly distributed seasonal occurrence of FP speak against a high prevalence of LB in this group of FP patients.

The causative agent of LB, *B. burgdorferi*, is heterogeneous in different parts of the world and also in different parts of Europe. Therefore, local studies on both the incidence and manifestations of LB and on the infestation rates of vectors of *B. burgdorferi sensu lato* are essential. Accumulating evidence suggests that *B. burgdorferi sensu stricto* is very rare or virtually absent on the mainland of Finland and along the eastern border. Our recent study has demonstrated that only *B. afzelii* and *B. garinii* could be isolated from ticks collected from popular parks of Helsinki. Similar results have been obtained in studies carried out in Russia and other parts of the former Soviet Union. Organotropism of different *Borrelia* genospecies may explain the varying clinical manifestations of LB in different geographic areas. The absence of *B. burgdorferi sensu stricto* on the Finnish mainland may explain the rarity of frank arthritis in our patients.

A seasonal pattern of LB-related FP was obvious in our study. This pattern was in accordance with the pattern found in previous studies, and it corresponded with the feeding periods of ticks. The highest incidence of LB occurred in September. Therefore, the threshold for suspecting LB in Finnish patients with FP must be set especially low during the late summer season.

Headache and arthralgia are well known symptoms of early LB. These symptoms were significantly more common in patients with definite LB than in other patients. Enlarged lymph nodes in the caudal portion of the parotid gland have previously been connected with FP caused by LB. Analogously, we found cervical lymph nodes significantly more common in patients with FP caused by LB than in other FP patients.

Idiopathic FP is presently considered to be caused by herpes simplex infection in majority of cases, which, along with other infectious causes of FP, may be responsible for enlarged regional lymph nodes. Thus, cervical lymphadenopathy alone may not be considered a specific sign for LB-caused FP. In logistic regression analysis the best model for explaining LB in our study was: presence of enlarged cervical lymph nodes, presence of arthralgia, and season of FP occurrence. This finding may help the clinician to diagnose FP linked to LB in areas endemic for LB.

According to previous reports, up to 80% to 90% of patients with idiopathic FP will recover completely. However, an analysis collated from 9 reports on FP in which the course of recovery was controlled in detail demonstrated complete recovery for only 54%. In cases with incomplete paralysis the recovery rate was 95% to 100%. In our study the facial nerve recovered completely in 57% of the patients. The final evaluation of recovery was based on the patients’ subjective reports, which indicated incomplete recoveries even in cases with minor complaints. The poorer recovery rate among women is difficult to explain on a basis of an actual difference between men and women; it may be due to a higher sensitivity of women in experiencing and reporting dysfunctions of facial movements.

The outcome of facial paralysis was slightly better in patients with LB than in patients with idiopathic FP. LB seems to cause a milder damage to the facial nerve than is the case in idiopathic FP, which is often caused by the herpes simplex virus. Two patients with the longest delay between the onset of FP and the initiation of the ceftriaxone medication (207 and 279 days) had the poorest outcome of FP in the LB group (House–Brackmann grade III). However, because of the limited number of the patients in LB group, any statistically relevant conclusions cannot be drawn.

With the logistic regression modeling, the best-fitting combination of variables to explain the poor recovery included total paralysis, history of previous FP, and hyperacusis. All these factors have been previously considered risk factors for a poor recovery from idiopathic FP.

Finnish and Swedish are the official languages in Finland. Six percent of the Finnish population belongs to the Swedish-speaking minority, which mostly lives in the south, southwestern, and west-coastal areas of the mainland of Finland and in the southern archipelago. The higher prevalence of positive levels of antibodies to *B. burgdorferi* in the Swedish-speaking patients is in accord with
the fact that these people more often live in areas highly endemic for LB.

PCR is a powerful method for detecting small amounts of specific microbial DNA, and it is obvious that only a few spirochetes in the tissues and body fluids are sufficient to cause the symptoms of LB. In the present study, however, the PCR test was not sensitive enough to detect borrelial DNA in the serum or CSF of the LB patients. Only one CSF sample was PCR-positive. Our poor success rate with the use of PCR in the diagnosis of LB is in agreement with the results of other studies.27

In the present study, most of the patients (9/11) with LB had CSF abnormalities. The most common abnormality (in 8/11 patients) was a positive level of CSF antibodies to B. burgdorferi, and one of these patients had antibodies only in the CSF. This finding emphasizes the importance of assessing CSF antibodies when LB is suspected in cases of FP. However, FP caused by LB can be present without abnormalities in the CSF.9,11

CONCLUSION

We observed 11 patients with LB among 503 consecutive patients with FP. This study shows that LB is an important infectious cause of FP. In addition to the use of laboratory diagnostic methods, special attention must be paid to a careful assessment of the patient’s medical history and to the possible clinical signs or symptoms related to LB. The measurement of serum antibodies to B. burgdorferi is currently the best method available for screening patients with FP. Seropositivity does not necessarily prove, however, a causal relationship between FP and LB. On the other hand, seronegativity does not rule out LB in these patients. In FP cases in which LB is suspected, the analysis of CSF is recommended.

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REFERENCES


