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Immunoglobulin M Immunoblot for Diagnosis of *Borrelia burgdorferi* Infection in Patients with Acute Facial Palsy

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We used immunoblotting to improve the specificity of the serologic diagnosis of Lyme borreliosis in cases of acute facial palsy. Twelve of 15 patients (80%) with suspected Lyme borreliosis, versus 0 of 10 controls, were positive by immunoglobulin M immunoblotting of acute-phase sera and 3 were negative, including 2 with borderline enzyme immunoassay results. Immunoglobulin M immunoblotting is a useful test to confirm *Borrelia burgdorferi* infection in patients with acute facial palsy and a positive enzyme immunoassay result.

Lyme disease, or Lyme borreliosis, is a tick-borne infection caused by the spirochete *Borrelia burgdorferi*. Several studies have reported facial palsy to be the most common physical sign of neurologic Lyme borreliosis (neuroborreliosis) (2, 12, 16). The proportion of facial palsy due to Lyme borreliosis on Long Island, New York, has been estimated to be 25% (8), and in a European study of children, 33% of acute facial palsy cases were due to Lyme borreliosis (4). Early and accurate diagnosis of *B. burgdorferi* infection as the cause of a facial palsy is important, as antibiotic treatment is indicated. In contrast, Bell's palsy is often treated with steroids, which may be deleterious in cases of infection. Accurate diagnosis is also important for prognostic reasons, as facial palsy may represent only one component of neuroborreliosis in some patients (11).

Currently, the accuracy of serodiagnosis of Lyme borreliosis is limited by the high rate of false-positive enzyme immunoassay (EIA) and immunofluorescence assay results, which can lead to overdiagnosis (7, 15). A positive or equivocal result should be confirmed by immunoblotting (6, 14). Although neurologic involvement in Lyme borreliosis is classically seen after several weeks to months of infection with *B. burgdorferi* (11), isolated facial palsy has been reported to occur earlier, at times concomitant with or preceding erythema migrans (EM) (5, 10). An immunoglobulin G (IgG) immunoblot may be negative in early Lyme borreliosis (6). We hypothesized that as facial palsy is usually an early manifestation of Lyme borreliosis, a diagnostic IgM immunoblot will be observed. Recently, an effort to improve the accuracy of serodiagnosis of Lyme borreliosis was undertaken (3). We used the proposed IgM immunoblot criteria to confirm *B. burgdorferi* infection in patients with acute facial palsy.

Patients. Patients with acute facial palsy seen at either the Long Island Jewish Medical Center's Lyme Disease Center, the University of Connecticut Health Center, or Winthrop University Hospital, and for whom serum was available, were studied. The study period was January 1992 to June 1994. Acute facial palsy was defined as facial palsy of less than 4 weeks' duration at the time serum was obtained. EIAs (total IgG and IgM antibody) for detection of antibodies to *B. burgdorferi* had been done on all sera. The test group consisted of 15 patients with positive EIAs (Lyme group), and the control group consisted of 10 patients with negative Lyme EIAs at the time of presentation with acute facial palsy. Seven Lyme group patients returned to provide convalescent-phase sera, which were drawn 4 to 13 weeks (mean, 7 weeks) after the acute-phase sera were drawn.

Immunoblotting. Separate IgM and IgG immunoblotting procedures were performed on all sera, as previously described (14). Briefly, low-passage *B. burgdorferi* B31, a sodium dodecyl sulfate–12.5% polyacrylamide separating gel, semidry electrophoretic transfer to nitrocellulose paper, and 1:100 dilutions of sera were used. The criteria for positive immunoblots were as follows: the presence of any 5 of 10 IgG bands [18, 23(OspC), 28, 30, 39, 41, 45, 58, 66, and 93 kDa] and the presence of any 2 of 3 IgM bands [23(OspC), 39, and 41 kDa].

Clinical features. Lyme group patients were 3.5 to 77 years old (mean, 28 years) (Table 1). The duration of facial palsy at the time serum was obtained ranged from 1 to 25 days (mean, 9.8 days). Three patients had EM; facial palsy followed EM by 2 weeks in two patients and by 4 months in one patient. The facial palsy was bilateral in two patients. Six of eight patients from whom spinal fluid was collected had abnormal cerebrospinal fluid (CSF) analysis results; three had pleocytosis, two had elevated CSF protein levels, and one had both of these abnormalities. Fourteen patients received antibiotic therapy (3 or 4 weeks' duration). In 13 patients, the facial palsy resolved completely by 8 weeks; one child had minimal paresis 11 months after onset, and one patient was lost to follow-up.

Control group patients were 4 to 16 years old (mean, 9.7 years). The duration of facial palsy at the time serum was obtained ranged from 1 to 28 days (mean, 6.2 days). All had unilateral facial palsy. Two of four patients from whom spinal fluid was collected had abnormal CSF analysis results; one had proven current *Mycoplasma pneumoniae* infection, and the other had Ramsay-Hunt syndrome. Other diagnoses were polyarteritis nodosa in one patient and Bell's palsy in seven. Five patients were treated with steroids, one received acyclovir, and four were given no treatment. The facial palsy resolved by 8 weeks after onset in nine patients, and one patient was lost to follow-up.

Acute-phase immunoblot. Twelve of 15 (80%) Lyme group serum samples were positive by IgM immunoblotting; the bands present are listed in Table 2. In contrast, none of the 10

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TABLE 1. Clinical features of acute facial palsy Lyme group

Patient no.	Age (yr), sex	Duration of palsy (days)	Month of presentation	EIA result[a]	Signs and symptoms other than facial palsy	CSF analysis result
1	6, F	7	July	1:1,280[b]	None	ND[c]
2	8, M	5	August	1:320[b]	None	ND
3	30, M	2	July	1.38/1.0	EM, headache, stiff neck (bilateral facial palsy)	Protein, 201 mg/dl
4	6, F	6	August	1.33/0.9	Fatigue, headache, neck and ear pain	ND
5	13, M	18	August	4.76/0.8	None	ND
6	3, F	5	June	1.8/0.8	None	ND
7	18, M	1	July	0.39/0.11	Headache, stiff neck	WBC,[d] 7/mm^3
8	66, F	11	October	1.13/0.9	Ear and face pain	Normal
9	60, F	20	July	4.6/1.0	Fatigue	Protein, 53 mg/dl
10	32, F	25	February	0.33/0.27	Joint pain and swelling associated with Crohn's disease	ND
11	77, M	17	June	0.60/0.50	Headache, stiff neck	Protein, 61 mg/dl
12	73, F	13	September	2.74/1.0	Headache, mental status changes	WBC, 623/mm^3; protein, 123 mg/dl
13	13, M	8	May	1.5/1.0	Fever, EM, impaired taste (bilateral facial palsy)	ND
14	11, F	3	October	0.16/0.12	EM 4 mo prior	Normal
15	9, F	7	July	0.37/0.13	Headache	WBC, 31/mm^3

[a] Results are in optical density units (patient/negative cutoff) unless otherwise noted.
[b] Result is expressed as a titer.
[c] ND, not determined.
[d] WBC, leukocyte.

control group serum samples were positive by IgM immunoblotting; no bands were seen for any specimen. Three of 15 (20%) Lyme group serum samples were positive by IgG immunoblotting, and all 10 control group serum samples were negative by IgG immunoblotting. The three IgM-negative Lyme group serum samples were also IgG negative.

Two Lyme group patients had borderline-positive Lyme EIA results (i.e., optical density of patient sample/optical density of negative-cutoff sample = 0.33/0.27 for patient 10 and 0.16/0.12 for patient 14). Both were among the three patients with negative IgM immunoblots. Patient 10 presented in February, with no history of a tick bite or rash. The IgG immunoblot was also negative for this serum specimen, which was drawn 25 days after the onset of facial palsy. Patient 14 had been tested for Lyme borreliosis because of a history of possible EM 4 months prior to the onset of facial palsy. However, the rash was not considered typical, and the IgG immunoblot was negative. Neither patient had received antibiotics.

Convalescent-phase immunoblot. Of seven patients for whom paired sera were available, six seroreverted to IgM negative 4 to 13 weeks after the onset of symptoms. The one that remained positive still had a positive IgM immunoblot at an 11-month follow-up visit. Six were positive by IgG immunoblotting, including three who had positive acute-phase specimens and three who first seroconverted 9 to 13 weeks after onset. One patient (patient 7) remained IgG immunoblot negative for a third serum specimen drawn 6 months after onset. Because of the presence of CSF pleocytosis, this patient was treated with intravenous ceftriaxone beginning the day after onset of facial palsy. This early treatment may have prevented a diagnostic IgG immunoblot response.

Comment. Lyme borreliosis can present as facial palsy alone.

TABLE 2. Immunoblot results for acute facial palsy Lyme group

Patient no.	Bands (kDa) seen and result obtained with immunoblotting specific for:			
	IgM		IgG	
	Acute phase	Convalescent phase	Acute phase	Convalescent phase
1	23, 41; positive	ND[a]	23, 28, 41, 66; negative	ND
2	23, 41; positive	ND	39, 41, 66; negative	ND
3	23, 41; positive	No bands; negative	39, 50, 66; negative	30, 39, 45, 58, 66; positive
4	23, 30, 39, 41, 45, 66, 93; positive	23, 41; positive	23, 39, 41, 45, 58, 66; positive	23, 39, 41, 45, 58, 66; positive
5	23, 30, 39, 41, 58, 66; positive	No bands; negative	41, 45, 58, 66; negative	28, 30, 39, 41, 45, 58, 66; positive
6	23, 41, 58, 66; positive	ND	41, 66; negative	ND
7	23, 30, 39, 41; positive	23; negative	23, 41, 45, 66; negative	23, 45, 66; negative
8	39, 41, 58, 66; positive	ND	66; negative	ND
9	23, 39, 41, 66; positive	23, 66; negative	23, 28, 39, 41, 45, 58, 66; positive	23, 28, 39, 41, 45, 58, 66; positive
10	No bands; negative	ND	66; negative	ND
11	39, 41, 58, 66; positive	ND	66; negative	ND
12	23, 41; positive	No bands; negative	23, 39, 66; negative	23, 39, 45, 58, 66; positive
13	39, 41, 45, 58, 66; positive	41, 66; negative	39, 41, 45, 58, 66; positive	30, 41, 45, 58, 66; positive
14	No bands; negative	ND	66; negative	ND
15	21; negative	ND	41; negative	ND

[a] ND, not determined.

The true proportion of cases of facial palsy that are attributable to *B. burgdorferi* infection in areas where the disease is endemic has been estimated at between 6 and 33%, although no study included immunoblot confirmation of the infection (1, 4, 8, 9, 13). Thus, empirical antibiotic treatment for all cases of acute facial palsy is not justifiable. Corticosteroids, which are often prescribed for idiopathic Bell's palsy, are unwarranted and perhaps deleterious in cases of infection (8). There are often no clinical clues to suggest Lyme borreliosis at presentation, and the palsy may even precede EM. False-positive EIA and immunofluorescence assay results are common. It is therefore important to have a confirmatory test available, one that has a high sensitivity at the time of initial presentation. In our study, IgG immunoblotting at initial presentation confirmed the presence of *B. burgdorferi* infection in only 3 of 15 patients suspected of having Lyme borreliosis on the basis of positive EIA results. In contrast, IgM immunoblotting was confirmatory in 12 of 15 patients (80%), and a negative immunoblot helped to exclude *B. burgdorferi* infection in at least 2 patients with a borderline EIA, and possibly in a third patient (patient 15) with a high EIA value. A false-positive EIA can arise from cross-reactive antibodies, most commonly antibodies to the 41-kDa polypeptide, and the serum of patient 15 demonstrated this band on IgG immunoblots. However, in the absence of a convalescent-phase specimen, it was not possible to be certain that patient 15 had a false-positive EIA. In clinical practice, a patient such as this should be treated with antibiotics and confirmation by convalescent-phase IgG immunoblotting should be attempted, although early treatment may prevent seroconversion.

Our findings underscore the disadvantage of relying solely on an EIA to diagnose Lyme borreliosis. EIA resulted in overdiagnosis of Lyme borreliosis, and the addition of IgM immunoblotting increased the accuracy of diagnosis by eliminating false-positive reactions.

We conclude that performing IgM immunoblotting in addition to an EIA provides specific confirmation of *B. burgdorferi* infection in patients presenting with acute facial palsy. Moreover, no false-positive IgM reactivity was seen in control subjects. The test is particularly useful in patients with a low clinical likelihood of Lyme borreliosis, such as one presenting in winter without a history of a tick bite or a rash, as it can distinguish true-positive and false-positive Lyme EIA results. Confirmation of *B. burgdorferi* infection facilitates optimal treatment decisions and alerts the physician to monitor for other symptoms and signs of Lyme borreliosis. Additionally, the results of our study support the notion of facial palsy as an early manifestation of Lyme borreliosis, one that commonly occurs within a month of onset of infection.

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