LYME BORRELIOSIS AND ACUTE PERIPHERAL FACIAL PALSY IN SLOVENIAN CHILDREN

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Abstract: To determine how often Slovenian children with acute peripheral facial palsy are infected with *Borrelia burgdorferi* sensu lato, 52 patients with peripheral facial palsy were included in this prospective clinical study. According to case definitions, the diagnosis of Lyme borreliosis was established in 56% of those patients. The diagnosis was confirmed in 41%, probable in 28%, and possible in 31% of patients.

Key Words: acute peripheral facial palsy, Lyme borreliosis, children, meningitis, intrathecal immunoglobulin synthesis pattern

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Slovenia is a highly endemic region for Lyme borreliosis (LB).[1] LB is a tick-borne multisystem infectious disease caused by *Borrelia burgdorferi* sensu lato.[2] Acute peripheral facial palsy (PFP) is a neurologic manifestation of the early disseminated stage of LB.[3] In Europe, PFP is detected more often in children than in adults and *B. burgdorferi* sensu lato is the leading cause of PFP in children.[4] Using strict laboratory criteria for diagnosis of LB, borrelial infection is confirmed in 19.3% of Slovenian adult patients with PFP.[5]

This study was performed to determine how often Slovenian children with PFP are infected with *B. burgdorferi* sensu lato.

MATERIALS AND METHODS

The prospective clinical study was conducted at the Department of Infectious Diseases, University Medical Centre Ljubljana, Slovenia, in 2004 and 2005. The study was approved by the Medical Ethics Committee of the Ministry of Health of the Republic of Slovenia. Informed consent was obtained from parents of all patients. Our patients were consecutive children younger than 15 years, hospitalized because of PFP. The patients were followed up for at least 6 months.

Medical history, physical examination, basic hematologic, biochemical, and microbiologic investigations, and lumbar puncture with cerebrospinal fluid (CSF) investigation were performed at the time of admission. Abnormal CSF findings were defined as reported previously.[6] CSF flow rate and the presence of intrathecal antibody production were defined according to the criteria reported by Reiber and Peter.[7] In blood and CSF concentrations of albumin and immunoglobulins G (IgG), A (IgA), and M (IgM) were determined. For each patient albumin (Q_{Alb}), IgG (Q_{IgG}), IgA (Q_{IgA}), and IgM (Q_{IgM}) CSF/serum quotient were calculated. We searched for intrathecal fraction (IF) of IgG (IgG_{IF}), IgA (IgA_{IF}), and IgM (IgM_{IF}).

Borrelial immunofluorescent assay (IFA) of IgM and IgG antibody titers without preabsorbtion were determined in serum and CSF as reported previously.[6] Titers $\geq$256 in serum and $\geq$16 in CSF were considered positive. Intrathecal specific antibody synthesis was determined by calculation of antibody index. Antibody index $>$1.4 was considered to be increased.[7] Borrelial serum antibodies measurements were repeated 1, 3, and 6 months after the enrolment into study.

Blood and CSF specimens were cultured in modified Kelly-Pettenkofer medium. Specimens were incubated at 33°C and examined by dark-field microscopy. Isolated strains of *B. burgdorferi* sensu lato were identified by polymerase chain reaction and/or by pulsed-field gel electrophoresis as reported previously.[8] DNA was restricted by *Mlu*I restriction enzyme.

The diagnosis of LB was established according to the case definitions used in our previous study.[6] Briefly, LB was confirmed by isolation of *B. burgdorferi* sensu lato from blood, from CSF, by seroconversion to borrelial antigens, by demonstration of borrelial intrathecal antibody production, by concomitant EM (clinically) or a combination of any of these. LB was considered probable in patients with positive but unchanging borrelial serum antibody titers and possible in patients with PFP and associated meningitis but without laboratory confirmation of borrelial infection.

Patients with PFP caused by LB were treated with intravenous ceftriaxone for 14 days.

Differences in categoric data were analyzed by the Yates corrected χ^2 test or Fisher exact test, whereas differences in continuous data were assessed by Kruskal-Wallis test and Wilcoxon rank sum test. All P values were 2-tailed; $P < 0.05$ was considered statistically significant.

RESULTS

During the 2-year period 52 patients (30 girls, 22 boys) fulfilled the inclusion criteria. The median age of the patients was 10.5 years with the range from 2 to 14.5. LB was established in 29 (56%) patients. In 23 (44%) patients, the cause of PFP remained unknown. Patients with LB were hospitalized between April and December with peak in June. Patients with PFP due to LB were younger than patients with PFP of unknown etiology (8 [2.5–14.5] vs. 12 [2–14.5] years, respectively; $P = 0.0171$). Bilateral PFP occurred in 1 (3%) patient with possible LB. There were no other differences regarding demographic and clinical features between the 2 groups (data not shown). On physical examination, meningeal signs were found more often in patients with PFP and LB. Symptoms and clinical signs in patients with PFP due to LB and due to unknown etiology are shown in Table 1.

The overall isolation rate of *B. burgdorferi* sensu lato from blood and CSF of patients with PFP was 5.8% (3/52) and 13.7% (7/51), respectively. All 7 isolates from CSF were identified as *B. garinii*. In 2 patients with positive CSF culture result, the culturing was performed on the day of the appearance of PFP. Time interval between the appearance of PFP and CSF culturing was 1 day in 1 patient, 2 days in 1 patient, and 4 days in the remaining 3 patients with positive CSF culture result. In 2 of 3 isolates from the blood, *Borreliae* did not grow well enough to enable identification of the genospecies. The third isolate was identified as *B. afzelii*.

At the time of admission to the hospital, positive serum IFA-IgM and/or IFA-IgG antibodies against *B. burgdorferi* sensu lato were found in 10 (34%) of 29 patients with LB. Positive serum IFA-IgG were detected in only 1 patient with confirmed LB. No patient with confirmed LB had positive serum IFA-IgM antibodies. On serologic follow-up, all patients with confirmed LB remained seronegative, except one with IFA-IgG seroconversion.

CSF pleocytosis was detected in 20 (69%) of 29 patients with PFP and LB. Of 12 patients 3 (25%) with confirmed LB and 6 (75%) of 8 patients with probable LB had no associated

TABLE 1. Symptoms and Clinical Signs in Patients With Acute Peripheral Facial Palsy due to LB and UE

Variable	LB	UE	*P*
Number	29	23	
Local and/or systemic symptoms*	15 (52)	11 (48)	1.0000
Local symptoms*	6 (21)	4 (17)	1.0000
Number of events (%)			
Pain	1 (3)	0 (0)	1.0000
Facial edema	2 (7)	2 (9)	1.0000
Eye redness	1 (3)	1 (4)	1.0000
Tearing	3 (10)	0 (0)	0.2455
Eye twitching	0 (0)	2 (9)	0.1908
Systemic symptoms*	11 (38)	8 (35)	0.9555
Number of events (%)			
Headache	5 (17)	3 (13)	1.0000
Fever	4 (14)	2 (9)	0.6821
Fatigue	4 (14)	2 (9)	0.6821
Malaise	4 (14)	0 (0)	0.1204
Myalgia	2 (7)	0 (0)	0.4970
Arthralgia	2 (7)	0 (0)	0.4970
Skeletal pain	2 (7)	0 (0)	0.4970
Neck pain	4 (14)	0 (0)	0.1204
Paresthesia	0 (0)	1 (4)	0.4423
Nausea	0 (0)	1 (4)	0.4423
Earache	2 (7)	1 (4)	1.0000
Collapse	1 (3)	0 (0)	1.0000
"Common cold"	0 (0)	2 (9)	0.1908
Taste disturbance	0 (0)	2 (9)	0.1908
Diarrhea	0 (0)	1 (4)	0.4423
Transitory blindness	0 (0)	1 (4)	0.4423
Poor appetite	1 (3)	0 (0)	1.0000
Clinical signs*	14 (48)	6 (26)	0.1781
Number of events (%)			
Solitary erythema migrans	2 (7)	0 (0)	0.4970
Positive meningeal signs	8 (28)	0 (0)	0.0064
Temperature ≥38°C	2 (7)	0 (0)	0.4970
Erythematous throat	1 (3)	3 (13)	0.3101
Otitis	1 (3)	2 (9)	0.5775
Conjunctivitis	1 (3)	1 (4)	1.0000
Lymphadenopathhy	1 (3)	1 (4)	1.0000
Tremor†	1 (3)	0 (0)	1.0000

LB indicates lyme borreliosis; UE, unknown etiology.
*Number of patients (%).
†Tick-borne meningoencephalitis excluded.

meningitis. All patients had lymphocytic pleocytosis. Elevated protein, albumin, total IgG, IgM, IgA, and decreased glucose concentration was detected in 30%, 30%, 30%, 65%, 25%, and 35% of patients with meningitis, respectively. About 55% of patients had elevated Q_{Alb} indicating a decreased CSF flow rate or blood-brain barrier dysfunction. Total IgM intrathecal antibody production was detected in 55% and IgA in 15% of patients. No patient had total IgG intrathecal antibody production; however, borrelial intrathecal IgG synthesis was detected in 1 patient, with specific antibody index of 15. Intrathecal immunoglobulin synthesis pattern $IgM_{IF} > IgA_{IF} > IgG_{IF}$ was characteristic for early Lyme neuroborreliosis.

According to the case definitions, the diagnosis of LB was confirmed in 12 (41%), probable in 8 (28%), and possible in 9 (31%) of 29 patients with LB (Table, Supplemental Digital Content 1, http://links.lww.com/INF/A230).

DISCUSSION

LB is the most frequent verified cause of PFP in children in Europe.[4,9,10] In present study, the diagnosis of LB was established in 56% of patients with PFP (Table, Supplemental Digital Content 1, http://links.lww.com/INF/A230). The cause of PFP remained unknown in 44% of the patients, since other diseases and microorganisms can occasionally cause PFP in children.[3,9,11]

Using strict laboratory criteria LB has been confirmed in 19.3% of Slovenian adult patients with PFP,[5] which does not differ significantly from the results in children presented in our study.

Patients with PFP associated with LB show associated symptoms more often than those with PFP resulting from other causes.[5,9,12,13] Our results do not confirm these findings; 52% of our patients with PFP due to LB complained about associated symptoms which was not significantly different from the patients with PFP of unknown etiology (Table 1).

Meningitis can be designated as the conditio sine qua non for diagnosis of Lyme neuroborreliosis.[10] We also included in our study, children with PFP and associated meningitis without microbiological confirmation of LB, as a group of possible LB. We agree that CSF pleocytosis in patients with PFP alone does not confirm the diagnosis of LB.[11,12] However, we believe that the possibility of LB in patients from endemic regions for LB (such as Slovenia), is high.

In clinical practice, the diagnosis of LB is most often based on clinical picture and measurement of specific antibody response.[10] If the initial result is negative, the test should be repeated to detect seroconversion.[11] Seroconversion is reported to contribute to 36.4% cases of confirmed borrelial infection in Slovenian adult patients with PFP.[5] On the contrary, seroconversion did not contribute to any single case of confirmed LB in Slovenian children.

Detection of borrelial intrathecal antibody production may help to establish the etiological diagnosis of PFP.[14] It is reported in 50% of Slovenian adult patients with PFP due to confirmed LB.[5] Possible reasons for low yield of specific intrathecal antibody production in our study were lumbar puncture performed early in the course of PFP (median of 2 days) or low sensitivity of microbiological methods used for detection of specific borrelial antibodies.

The diagnosis of LB in Slovenian adult patients with PFP has been confirmed by isolation of *B. burgdorferi* sensu lato from CSF in 13.6%.[5] In our patients with confirmed LB, it was 58% which is one of the highest reported in the literature so far.[14]

Finding of *B. afzelii* in the blood of one of our patients with PFP is, to our knowledge, the first report in the literature.

In conclusion, LB was established in 56% of Slovenian children with PFP. The diagnosis of LB was confirmed in 41%, probable in 28%, and possible in 31% of patients.

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