

Comparison of Culture-Confirmed Erythema Migrans Caused by *Borrelia burgdorferi* sensu stricto in New York State and by *Borrelia afzelii* in Slovenia

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Background: The clinical manifestations of Lyme borreliosis in North America and Europe seem to differ, but a systematic comparison has never been done.

Objective: To compare European and U.S. patients with culture-confirmed erythema migrans.

Design: Prospective, clinical cohort study.

Setting: University medical centers in Westchester County, New York, and Ljubljana, Slovenia.

Patients: 119 U.S. patients with *Borrelia burgdorferi* sensu stricto infection and 85 Slovenian patients with *B. afzelii* infection.

Measurements: Interview, physical examination, and laboratory assays.

Results: Compared with Slovenian patients, U.S. patients had erythema migrans for a briefer duration (median duration, 4 days compared with 14 days; $P < 0.001$) but were more likely to have systemic symptoms ($P = 0.01$), abnormal findings on physical examination ($P < 0.001$), and seroreactivity ($P < 0.001$). Central clearing of erythema migrans lesions was more likely in Slovenian patients ($P < 0.001$).

Conclusions: Erythema migrans caused by *B. afzelii* in Slovenia and erythema migrans caused by *B. burgdorferi* in New York have distinct clinical presentations. Caution should be used when clinical and laboratory experience from one side of the Atlantic is applied to patients on the other.

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The clinical presentations of Lyme borreliosis in the United States and Europe seem to differ (1-7). For example, European patients with Lyme borreliosis may develop certain skin manifestations (acrodermatitis chronica atrophicans and borrelial lymphocytoma) that are extremely rare or nonexistent in the United States (6, 7). One explanation of such differences may be the recently appreciated variation in strains of *Borrelia* species between the two continents (7-9). All isolates from U.S. patients have thus far been members of the genomic group *Borrelia burgdorferi* sensu stricto (henceforth referred to as *B. burgdorferi*), whereas European isolates have included two additional genospecies, *B. garinii* and *B. afzelii*. Until now, however, no reports of clinical disparities have been based on the systematic study of large numbers of patients with culture-confirmed infection.

To investigate possible differences in the manifestations of Lyme borreliosis in Europe and the United States, we compared epidemiologic, demographic, clinical, and laboratory findings in patients from New York State and patients from Slovenia who had microbiologically confirmed erythema migrans caused by *B. burgdorferi* and *B. afzelii*, respectively.

Methods

Patients

To isolate *Borrelia* species from clinical specimens, we recruited patients with a clinical diagnosis of erythema migrans in two separate prospective studies. The Centers for Disease Control and Prevention surveillance definition of erythema migrans (10) was satisfied in almost all cases, although three Slovenian patients with erythema migrans lesions less than 5 cm in diameter were enrolled. Patients from the United States were seen at the Lyme Disease Diagnostic Center, Westchester Medical Center, Valhalla, New York, from June 1991 through August 1995. Slovenian patients were evaluated at the Lyme Borreliosis Outpatient Clinic, Ljubljana, Slovenia, in 1993. All patients were older than 15 years of age and gave informed consent. Patients were included in the present study if *Borrelia* organisms were recovered from their skin specimens. Several U.S. patients had repeated culture-

Table 1. Characteristics of Patients with Culture-Confirmed Erythema Migrans

Characteristic	Patients in Slovenia with <i>Borrelia afzelii</i> (n = 85)	Patients in United States with <i>Borrelia burgdorferi</i> (n = 119)	P Value*
Male, n (%)	33 (38.8)	70 (58.8)	0.007
Median age (range), y	48 (16–74)	40 (16–76)	<0.001
Tick bite at rash site recalled, n (%)†	54 (63.5)	30 (25.2)	<0.001
Median time from bite to rash onset (range), d	17 (1–150)	11 (1–55)	0.07
Median duration of rash at presentation (range), d	14 (1–206)	4 (1–39)	<0.001
Median size of lesions at presentation (range), cm	16 (4–60)	14 (5–73)	>0.2
Multiple lesions, n (%)†	6 (7.1)‡	16 (13.4)§	>0.2
Location of primary lesion, n (%)†			
Leg	44 (51.8)	40 (33.6)	0.01
Arm and shoulder	18 (21.2)	17 (14.3)	>0.2
Trunk and abdomen	23 (27.1)	60 (50.4)	<0.001
Head and neck	0	2 (1.6)	>0.2
Central clearing of erythema migrans lesion, n (%)†	58 (68.2)	36 (35.3)¶	<0.001
Local symptoms at erythema migrans lesion, n (%)†	44 (51.8)	50 (49.0)¶	>0.2
Pruritus	36 (42.4)	41 (40.2)¶	>0.2
Pain or burning	16 (18.8)	35 (34.3)¶	0.02

* Qualitative data were analyzed by using the chi-square test (Yates corrected) or the Fisher exact test; quantitative data were analyzed by using the median test. All results are two-tailed.

† Values are the number (percentage) of patients.

‡ Range, 2 to 44 lesions.

§ Range, 2 to 70 lesions.

|| Leg includes hip; trunk and abdomen includes axilla and groin.

¶ Rash characteristics described for 102 of 119 (85.7%) U.S. patients.

confirmed episodes of erythema migrans in separate years; for each of these patients, only the first episode was included.

Laboratory Methods

All isolates were obtained from biopsy or needle aspiration of erythema migrans lesions (11, 12). Cultures were processed as previously reported in modified Barbour–Stoenner–Kelly medium (11) for U.S. patients and modified Kelly–Pettenkofer medium (12) for Slovenian patients. At the U.S. study site, we identified spirochetes as *B. burgdorferi* by using polymerase chain reaction (PCR) with specific primers directed at the ribosomal RNA genes of *Borrelia* species (13). We identified the species of European isolates by using two independent methods: 1) species-specific PCR with different oligonucleotide primer sequences (14) and 2) pulsed-field gel electrophoretic separation of restriction enzyme MluI digestion fragments (15) (the pattern of large restriction fragments produced is diagnostic of the species). Because most Slovenian isolates by far were *B. afzelii* (12), cases of erythema migrans due to other species (including four cases due to *B. burgdorferi* and six due to *B. garinii*) were excluded. Complete blood counts were done, liver function tests were performed, and the erythrocyte sedimentation rate was measured at the time when cultures were obtained.

Baseline serum specimens were tested for antibodies to *B. burgdorferi*. Convalescent-phase specimens were obtained after 1 week to 1 month for U.S. patients and after 2 months for Slovenian patients. In the United States, serum specimens were tested for antibodies to *B. burgdorferi* with a poly-

valent enzyme-linked immunosorbent assay (Whittaker Bioproducts, Inc., Walkersville, Maryland) (11, 16). In Slovenia, the presence of serum IgM and IgG antibodies to *B. afzelii* was determined separately by immunofluorescent assay without preabsorption (17); a local skin isolate of *B. afzelii* was used as antigen. Titers of 1:256 or more were considered to indicate positivity.

Statistical Analysis

Differences in quantitative data were analyzed by using the median test, and differences in qualitative data were analyzed by using the chi-square test (with the Yates correction) or the Fisher exact test. We used Epi-Info 6 for all analyses (Statcalc, version 6.04a, Centers for Disease Control and Prevention, Atlanta, Georgia). All *P* values were two-tailed.

Results

Borrelia afzelii was recovered from the skin specimens of 85 Slovenian patients; none of these patients had been reported previously. *Borrelia burgdorferi* was cultured from 119 U.S. patients; 77 of these patients had been reported previously (11). Of the U.S. isolates, 30 were randomly selected for species identification by PCR, and all 30 were identified as *B. burgdorferi*. Thus, it is likely (although not certain) that the remainder of the isolates were also *B. burgdorferi*.

Demographic patient data and the characteristics of erythema migrans are summarized in **Table 1**. All Slovenian patients and 113 of 119 U.S. patients (95%) were white. Slovenian patients were more

likely than U.S. patients to recall a tick bite at the erythema migrans site (63.5% compared with 25.2%; $P < 0.001$). Although the size of the erythema migrans lesions was similar in the two groups of patients, the median duration of erythema migrans at presentation was longer (14 days [range, 1 to 206 days] compared with 4 days [range, 1 to 39 days]; $P < 0.001$) and central clearing was more common (68.2% compared with 35.3%; $P < 0.001$) in Slovenian patients than in U.S. patients. Localized pain or burning at the erythema migrans site was more common in U.S. patients (34.3% compared with 18.8%; $P = 0.02$). The occurrence of multiple erythema migrans lesions was greater in the U.S. patients than in the Slovenian patients, but the difference was not significant (13.4% compared with 7.1%; $P > 0.2$).

Patients in the United States were more likely than those in Slovenia to have systemic symptoms (68.9% compared with 50.6%; $P = 0.01$), including fatigue (54.6% compared with 32.9%; $P = 0.003$), myalgia (44.5% compared with 21.1%; $P = 0.001$), fever or chills (37.8% compared with 8.2%; $P < 0.001$), and stiff neck (38.7% compared with 8.2%; $P < 0.001$) (Table 2). Objective findings on

physical examination were also more common in U.S. patients (57.1% compared with 14.1%; $P < 0.001$) and most frequently manifested as regional lymphadenopathy (seen in 28.6% of U.S. patients compared with 8.2% of Slovenian patients; $P < 0.001$) or fever (body temperature ≥ 37.8 °C) (seen in 15.1% of U.S. patients compared with 1.2% of Slovenian patients; $P < 0.001$). Slovenian patients were more likely to have hepatomegaly (5.9% compared with 0; $P = 0.01$), but U.S. patients more often had at least one abnormal result on a liver function assay (32.2% compared with 18.3%; $P = 0.04$), were more likely to have erythrocyte sedimentation rates two or more times the upper limit of normal (25% compared with 3.7%; $P < 0.001$), were more likely to seroconvert (84.2% compared with 10.9%; $P < 0.001$), and were more often seropositive at presentation (35.3% compared with 22.4%; $P = 0.07$).

Discussion

Our findings establish what has long been believed: Some of the clinical and laboratory features

Table 2. Selected Clinical and Laboratory Findings in Patients with Culture-Confirmed Erythema Migrans

Variable	Patients in Slovenia with <i>Borrelia afzelii</i> (n = 85)	Patients in United States with <i>Borrelia burgdorferi</i> (n = 119)	P Value
	n (%)		
Symptomst			
Fatigue	28 (32.9)	65 (54.6)	0.003
Arthralgia	23 (27.1)	48 (40.3)	0.07
Myalgia	18 (21.2)	53 (44.5)	0.001
Headache	24 (28.2)	46 (38.7)	0.1
Fever or chills	7 (8.2)	45 (37.8)	<0.001
Stiff neck	7 (8.2)	46 (38.7)	<0.001
Any systemic symptom	43 (50.6)	82 (68.9)	0.001
Physical examination findings†			
Lymphadenopathy	8 (9.4)	46 (38.7)	<0.001
Regional	7 (8.2)	34 (28.6)	<0.001
Generalized	1 (1.2)	12 (10.1)	0.02
Fever	1 (1.2)	18 (15.1)	<0.001
Tenderness on neck flexion	7 (8.2)	14 (11.8)	>0.2
Joint swelling	3 (3.5)	1 (0.8)	>0.2
Joint tenderness	4 (4.7)	9 (7.6)	>0.2
Hepatomegaly	5 (5.9)	0	0.01
Any abnormal finding	12 (14.1)	68 (57.1)	<0.001
Laboratory findings§			
Erythrocyte sedimentation rate ≥ 2 times the upper limit of normal	3/82 (3.7)¶	28/112 (25.0)¶	<0.001
Alanine aminotransferase level >40 U/L	11/82 (13.4)¶	25/118 (21.2)¶	0.2
Alkaline phosphatase level >117 U/L	7/82 (8.5)¶	17/118 (14.4)¶	>0.2
Any elevated result on a liver function assay**	15/82 (18.3)¶	38/118 (32.2)¶	0.04
Positive result on a serologic test at baseline††	19/85 (22.4)¶	42/119 (35.3)¶	0.07
Seroconversion (negative to positive)††	7/64 (10.9)¶‡	64/76 (84.2)¶‡‡	<0.001
Seropositivity††	26/85 (30.6)¶‡	106/119 (89.1)¶‡‡	<0.001

* Analyzed by using the chi-square test (with Yates correction) or the Fisher exact test. All results are two-tailed.

† No significant difference was seen between the two groups in the occurrence of anorexia, dizziness, nausea or vomiting, memory or concentration disturbance, or cough.

‡ No significant difference was seen between the two groups in the occurrence of conjunctivitis, and no patient had splenomegaly.

§ No significant difference was seen between the two groups in the occurrence of anemia, leukocytosis, leukopenia, or thrombocytopenia.

|| 40 mm/h or more for women; 20 mm/h or more for men (Westergren method).

¶ Patients with abnormal value/patients who had test performed.

** Assay for alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, or γ -glutamyltranspeptidase.

†† IgM/IgG immunofluorescent assay (Slovenia) or polyvalent enzyme-linked immunosorbent assay (United States).

‡‡ Three patients (two from Slovenia and one from the United States) had no convalescent-phase serologic testing performed.

of Lyme disease differ in the United States and Europe. The differences seem to result, in part, from a tendency for *B. afzelii* to be less virulent than *B. burgdorferi*. Slovenian patients with *B. afzelii* were significantly less likely than U.S. patients with *B. burgdorferi* to be systemically ill (Table 2) and to have fever ($P < 0.001$) or regional lymphadenopathy ($P < 0.001$) on physical examination. Although the duration of erythema migrans at presentation was longer in Slovenian patients, lesion size in Slovenian patients was similar to that in U.S. patients; this implies that *B. afzelii* spreads more slowly in the skin (11). Because central clearing occurs, in part, as a function of time (2), its higher frequency in Slovenian patients (68.2% compared with 35.3%; $P < 0.001$) is probably related to the longer duration of erythema migrans at presentation. Nonetheless, in contrast to what might have been anticipated from earlier reports (1–6, 18), dissemination to multiple cutaneous sites did not occur significantly more often in U.S. patients than in Slovenian patients in our study ($P = 0.2$).

Our observations in patients in Westchester County, New York, agree with those of other studies of North American patients with erythema migrans (1, 4, 5), in which reported rates of systemic illness are often greater than 75%. In contrast, reported rates of systemic illness in Europe are often less than 35% (2, 3, 8).

In our study, Slovenian patients were much less likely than U.S. patients to be seropositive (26 of 85 [30.6%] compared with 106 of 119 [89.1%]; $P < 0.001$), principally because seroconversion was less common (7 of 64 patients [10.9%] compared with 64 of 76 patients [84.2%]; $P < 0.001$). The seroconversion rate in our U.S. patients, however, was similar to that seen in other recent studies of U.S. patients with erythema migrans (5). Moreover, the contrasting rates of seropositivity at presentation were particularly evident when patients with longstanding erythema migrans (duration ≥ 14 days) were compared; 94% of such patients in the United States (15 of 16) but only 28% of such patients in Slovenia (13 of 47) were seropositive ($P < 0.001$). With rare exceptions (19), European studies have reported low rates of seropositivity (20% to 50%) in patients with erythema migrans (3, 18), despite a long duration of illness (often longer than several weeks) (3). However, because convalescent-phase serologic samples from Slovenian patients were obtained at 2 months (rather than at 1 week to 1 month, as in U.S. patients), some cases of seroconversion may have been missed. Furthermore, the use of different methods in different laboratories may have contributed to different rates of seroreactivity.

In numerous European countries, *B. afzelii* has

predominated among isolates recovered from patients with erythema migrans (7–9, 12, 18). In the United States, the only species isolated from clinical specimens to date is *B. burgdorferi* (8). Preliminary evidence from European studies (7–9, 14) suggests that Lyme borreliosis is associated with different clinical presentations, depending on the *Borrelia* genotype involved. The greater heterogeneity of *Borrelia* species in Europe also has important implications for vaccine development: It is unlikely that the single antigen preparation studied in the United States, which is derived from *B. burgdorferi sensu stricto*, will be effective in Europe (20).

It is therefore likely that the differences seen in our two groups of patients with erythema migrans were principally due to differences between illness caused by *B. afzelii* and illness caused by *B. burgdorferi* and that our U.S. patients would have been very similar to European patients whose disease was associated with *B. burgdorferi*. The clinical differences noted, however, could also have been influenced by a varying incidence of co-infection with any of several other tick-borne pathogens; this is a topic of ongoing investigation (21).

Our comparative study of Lyme borreliosis in Europe and North America was confined to early disease associated with erythema migrans because of the readily recognizable clinical and microbiologic markers of this condition. Our findings in a large, prospective series of culture-confirmed patients suggest that Lyme borreliosis in Europe and in the United States consists of at least two distinct syndromes that are caused by different agents and are associated with different clinical and serologic presentations. Caution should be used when clinical and laboratory experience from one side of the Atlantic is applied to patients on the other.

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