Clinical Infectious Diseases

MAJOR ARTICLE

Course and Outcome of Early European Lyme Neuroborreliosis (Bannwarth Syndrome): Clinical and Laboratory Findings

Katarina Ogrinc,[1] Lara Lusa,[2] Stanka Lotrič-Furlan,[1] Petra Bogovič,[1] Daša Stupica,[1] Tjaša Cerar,[3] Eva Ružić-Sabljić,[3] and Franc Strle[1]

[1]Department of Infectious Diseases, University Medical Center Ljubljana, Institutes for [2]Biostatistics and Medical Informatics, and [3]Microbiology and Immunology, Medical Faculty, University of Ljubljana, Slovenia

(See the Editorial Commentary by Halperin on pages 354–5.)

Background. Information on the course and outcome of early European Lyme neuroborreliosis is limited.

Methods. The study comprised 77 patients (38 males, 39 females; median age, 58 years) diagnosed with painful meningoradiculitis (Bannwarth syndrome) who were followed up for 1 year at a single center.

Results. Duration of neurological symptoms before diagnosis was 30 (interquartile range, 14–50) days. The most frequent symptoms/signs were radicular pain (100%), sleep disturbances (75.3%), erythema migrans (59.7%), headache (46.8%), fatigue (44.2%), malaise (39%), paresthesias (32.5%), peripheral facial palsy (PFP) (36.4%), meningeal signs (19.5%), and pareses (7.8%). Cerebrospinal fluid (CSF) analysis revealed lymphocytic/monocytic pleocytosis, elevated protein concentration, and intrathecal synthesis of borrelial immunoglobulin M and immunoglobulin G antibody in 100%, 81.1%, 63%, and 88.7% of patients, respectively. Borreliae (predominantly *Borrelia garinii*) were isolated from CSF, skin, and blood in 15.6%, 40.6%, and 2.7% of patients, respectively. The outcome after 14-day treatment with ceftriaxone was favorable in 87.8% of patients. Control CSF examination at 3 months showed decreased leukocyte counts in all patients; however, 23.3% still had pleocytosis ($>10 \times 10^6$ cells/L). A model based on pretreatment data and the findings at the end of 14-day antibiotic treatment accurately predicted which patients would have an unfavorable outcome 6 or 12 months after treatment.

Conclusions. Our patients had fewer pretreatment neurological complications (PFP, pareses) than reported for Bannwarth syndrome decades ago, probably as the result of earlier recognition and prompt antibiotic treatment. Unfavorable outcome was rare and was predicted by the continued presence of symptoms 14 days after commencement of treatment.

Keywords. Lyme neuroborreliosis; Bannwarth syndrome; *Borrelia burgdorferi* sensu lato; *Borrelia garinii*; outcome.

Bannwarth syndrome (BS) is a typical manifestation of early Lyme neuroborreliosis (LNB) in Europe. It is characterized by painful radiculoneuritis and lymphocytic pleocytosis in the cerebrospinal fluid (CSF), often associated with cranial nerve involvement and sometimes with peripheral paresis [1–4]. In a substantial proportion of patients the syndrome is preceded by an erythema migrans (EM) [4–7]. BS was reported several decades before the etiology of Lyme borreliosis (LB) was established [2, 8–10]. Later, several analyses of mostly small series of patients (7–100) with BS were published; however, all but 1 (comprising 11 patients) [11] date from >20 years ago [4–7, 12–19].

The aim of this prospective study was to obtain clinical and laboratory data on the course and outcome of patients with BS and to determine characteristics associated with unfavorable outcome.

Received 27 November 2015; accepted 6 April 2016; published online 8 May 2016.
Correspondence: K. Ogrinc, Japljeva 2, 1525 Ljubljana, Slovenia (katarina.ogrinc@kclj.si).

Clinical Infectious Diseases® 2016;63(3):346–53

DOI: 10.1093/cid/ciw299

PATIENTS AND METHODS

The study was approved by the Medical Ethics Committee of the Ministry of Health of the Republic of Slovenia (35/08/06).

Patients

Adult patients with a clinical diagnosis of BS (defined by the presence of radicular pain (RP) and CSF lymphocytic pleocytosis) attending our LB outpatient clinic between November 2005 and October 2013 were included in the study.

Clinical Evaluation

Demographic, epidemiologic, and clinical data were obtained using a structured questionnaire. Data on previous antibiotic treatment, tick bites, and the presence of EM within 4 months before the onset of pain were of particular interest. EM was defined in accordance with criteria reported previously [20]. The location of RP was recorded. After responding to open questions, patients were asked to score the intensity of each present symptom (that had newly developed or intensified since the beginning of the current illness and had no other obvious explanation) on a scale from 1 to 10. In clinical examination, particular attention was paid to EM, its location, diameter,

and type (diffuse or ring-like), and signs of neurological involvement (meningeal signs, peripheral facial palsy [PFP] or other cranial nerve involvement, sensory/motor deficit, tremor). Patients were followed up at outpatient visits at 14 days and at 3, 6, and 12 months after the beginning of antibiotic treatment.

Laboratory Evaluation

Routine blood analyses were performed. CSF was tested for cell counts and levels of protein and glucose; a leukocyte count $>5 \times 10^6$ cells/L (pleocytosis) and protein concentration >0.45 g/L were considered abnormal findings. Immunoglobulin classes G and M (IgG and IgM, respectively) and albumin levels were determined in serum and CSF, and the corresponding quotients were calculated. Quotients of IgG and albumin were interpreted as abnormal when they were above 0.0035 and 0.0074, respectively. The majority of patients underwent electrocardiography at the initial visit. A control lumbar puncture was performed at the 3-month follow-up visit.

Serological Evaluation

Antibodies to *Borrelia burgdorferi* sensu lato in serum and CSF were determined using an indirect chemiluminescence immunoassay (LIAISON, Diasorin, Italy) with recombinant antigens OspC and VlsE for detection of IgM antibody and VlsE for IgG. Results were graded according to the manufacturer's instructions. Intrathecal synthesis of borrelial antibodies was determined as described by Reiber and Peter: antibody index values >1.4 were interpreted as indicating intrathecal production of borrelial antibodies [21].

In the large majority of patients, serum IgM and IgG antibodies to tick-borne encephalitis virus were also determined, using Enzygnost Anti-TBEV (IgM, IgG) kits (Dade Behring Marburg GmbH, Marburg, Germany) according to the manufacturer's instructions.

Cultivation and Typing of *B. burgdorferi* Sensu Lato

Modified Kelly-Pettenkofer (MKP) medium was used for cultivation of *B. burgdorferi* sensu lato from blood, CSF, and skin specimens as described elsewhere [22]. CSF (1 mL) samples were obtained from all patients; blood (9 mL) samples from 75 of 77 patients. Skin biopsies were taken from patients who had EM in the course of the disease and consented to the procedure; the samples ($2.5 \times 2 \times 2$ mm) were taken at the border of the EM or, when EM had already disappeared, at the site of past EM. CSF and skin samples were inoculated directly into tubes containing 7 mL MKP medium. Blood samples were centrifuged and 1-mL samples of plasma were inoculated into tubes containing 7 mL MKP medium. All samples were cultivated at 33°C and examined weekly by dark-field microscopy for the presence of spirochetes (up to 9 weeks for skin and CSF samples, 12 weeks for blood). Isolates were identified to species/strain level using pulsed-field gel electrophoresis after *MluI* restriction of genomic DNA or by polymerase chain reaction–based restriction fragment-length polymorphism of the intergenic region [23, 24].

Treatment

Patients were treated with ceftriaxone 2 g daily intravenously or with oral doxycycline 100 mg twice daily for 2 (exceptionally 3) weeks.

Definition of Outcome

The outcome was defined as follows:

- Complete recovery: complete regression of symptoms/signs of the disease.
- Pronounced improvement: marked regression of symptoms/signs of the disease, which are present only occasionally and/or have low intensity, not demanding regular use of analgesics and not interfering with daily activities.
- Partial improvement: partial regression of symptoms/signs, which still require substantial quantities of analgesics and/or significantly influence daily activities.
- Failure: persistence, intensification, or appearance of new symptoms/signs, and/or positive posttreatment CSF, skin, or blood cultures for borreliae.

Unfavorable long-term clinical outcome was defined as partial improvement or failure at 6 or 12 months after enrollment; all other patients were classified as having a favorable outcome.

Retreatment

Patients were retreated in cases of unsatisfactory clinical response to the first antibiotic treatment, persistence of CSF pleocytosis ($>10 \times 10^6$ cells/L), and/or positive posttreatment CSF, blood, or skin cultures for borreliae. A 2-week course of ceftriaxone or doxycycline was used, as above.

Statistical Methods

Numerical data were summarized with medians and interquartile ranges; categorical data with frequencies and proportions. Medians and proportions were reported with 95% confidence intervals.

The characteristics of patients with favorable and unfavorable outcomes were compared using univariate logistic regression with Firth penalty [25]. The variables (predictors) compared included characteristics at enrollment (demographic data, clinical characteristics, CSF findings, serological and culture results) and the presence of individual signs/symptoms at the first follow-up visit (14 days after enrollment); the variables were selected using expert opinion (K. O., F. S.), independent from the observed outcomes. Results were summarized with odds ratios, their 95% confidence intervals, and *P* values.

A model for the prediction of outcome was built, with inclusion of all the predictors and using penalized logistic regression with ridge penalty; this model is preferable to logistic regression when a large number of potentially correlated predictors is considered. The complexity parameter, which determines the amount of shrinkage, was estimated with cross-validation. Results were summarized with penalized odds ratios, and the

Table 1. Demographic, Epidemiologic, and Clinical Findings in 77 Patients With Bannwarth Syndrome

Characteristic	No. (%) of Patients or Median (IQR)	95% CI for % or Median
Male sex	38 (49.3%)	38.0%–61.0%
Age, y	58 (49–67)	54–60
Annual No. of tick bites	1 (1–5)	2.5–5.5
EM	46 (59.7%)	47.9%–70.8%
Solitary	42 (54.5%)	43.0%–66.0%
Multiple	4 (5.2%)	1.0%–13.0%
Onset of EM, d[a]	17 (6–45)	14.5–43
Antibiotic therapy[a]	17 (22.1%)	13.0%–33.0%
Antibiotic therapy for EM[a]	15/46 (32.6%)	19.5%–48.0%
Duration of illness[b], d[a]	30 (14–60)	26.5–40.5
Duration of neurologic symptoms, d[a]	30 (14–50)	25–39
Radicular pain matching the site of (past) EM[a]	33/46 (71.7%)	57.0%–84.0%
Findings at presentation		
EM or multiple EM	22 (28.6%)	19.0%–40.0%
Ring-like EM	10/22 (45.5%)	24.0%–68.0%
Largest diameter of EM, cm	35 (25.5–46.5)	27.5–58.5
Lymphocytoma	1 (1.3%)	0%–7.0%
Fever (>38°C)	0	0%–5.0%
Meningeal signs	15 (19.5%)	11.0%–30.0%
Peripheral facial palsy	28 (36.4%)	26.0%–48.0%
Bilateral facial palsy	3/28 (10.7%)	2.3%–28.2%
Pareses	6 (7.8%)	3.0%–16.0%
Tremor	3 (3.9%)	1.0%–11.0%

Abbreviations: CI, confidence interval; EM, erythema migrans; IQR, interquartile range.

[a] In the course of the illness up to enrollment.

[b] Time from first symptoms/signs of illness except for EM.

Table 2. Location of Radicular Pain According to Location of the Skin Lesion in 46 Patients with Bannwarth Syndrome Who Had Erythema Migrans in the Course of the Disease

Location of EM	Location of Radicular Pain				
	Neck	Arm[a]	Trunk	Leg[b]	Total
Neck	0	0	1 1/1 (100) 1/28 (0.4)	0	1 (2.2)
Arm[a]	1 1/7 (14.3) 1/1 (100)	2 2/7 (28.6) 2/2 (100)	3 3/7 (42.8) 3/28 (10.7)	1 1/7 (14.3) 1/15 (0.7)	7 (15.2)
Trunk	0	0	18 18/19 (94.7) 18/28 (64.3)	1 1/19 (5.3) 1/15 (0.7)	19 (41.3)
Leg[b]	0	0	6 6/19 (31.6) 6/28 (21.4)	13 13/19 (68.4) 13/15 (86.7)	19 (41.4)
Total	1 (2.2)	2 (4.3)	28 (60.9)	15 (32.6)	46

Data are presented as No. (%) of patients, with total, row %, column %. In patients with multiple erythema migrans (EM), the location of primary EM was considered. There were no patients with EM or radicular pain (RP) located on the head. In individuals with correlation between the sites of EM and RP, comparable dermatomes were affected. Patients in whom radicular symptoms did not localize to the anatomic region of the EM had no indications suggesting more disseminated disease (all 13 had solitary EM; the frequency of systemic symptoms was comparable to patients with matched EM and RP location).

Abbreviation: EM, erythema migrans.

[a] Including axillary region.

[b] Including inguinal region.

cross-validated area under the receiver operating characteristic curve (AUC) was obtained with leave-one-out cross-validation.

R statistical language was used for all the analyses [26]. The penalized models were fitted using the glmnet R package [27]. The logistf R package was used to apply Firth correction in logistic regression analysis [25].

RESULTS

During the 8-year period, 77 patients with a clinical diagnosis of BS were enrolled in the study: 38 males (49.3%) and 39 females (50.7%), with a median age of 58 (range, 21–78) years. Their basic demographic, epidemiologic, and clinical data are shown in Table 1. Table 2 shows the location of RP and preceding or accompanying EM; the locations matched in 33 of 46 (71.7%) patients. CSF findings at enrollment and 3 months later, together with *B. burgdorferi* sensu lato serological and culture results, are shown in Table 3.

Basic laboratory test results were within normal range in the majority of patients, abnormalities being rare and mild. Electrocardiography, in 58 of the patients, revealed atrioventricular block in 4; 3 of them (all with first-degree block) had a chronic heart condition already present well before borrelial infection. One patient, with complete atrioventricular block, was admitted to hospital. The accompanying RP pointed to borrelial etiology and prompted CSF examination that demonstrated lymphocytic pleocytosis; the heart block was completely reversible.

A total of 72 patients were treated with ceftriaxone for 2 weeks; 2 more patients were treated for 3 weeks. Oral doxycycline was prescribed in 3 patients because of allergy to ceftriaxone (in 2 patients) or refusal of parenteral therapy (1 patient).

Compliance of patients with follow-up visits was 100% at 2 weeks, 98.7% at 3 months, and 97.4% at 6 and 12 months. Their subjective assessment of treatment efficacy is shown in Figure 1. The frequency and intensity of symptoms and the frequency of clinical signs gradually diminished (Table 4; Figure 2). The CSF analysis and *B. burgdorferi* sensu lato serological and culture results at the 3-month follow-up, together with comparison with the pretreatment results, are shown in Table 3 (see also Supplementary Figure 1). In patients with positive results in pretreatment CSF, blood, or skin cultures, the corresponding follow-up cultures for borreliae were all negative.

Antibiotic therapy was repeated within 3–6 months in 20 of 77 (26%) patients because of unsatisfactory clinical response to the first treatment (3 patients), persistence of CSF cell count $>10 \times 10^6$ cells/L (8 patients), or both (9 patients).

Unfavorable long-term clinical outcome was observed in 9 of 74 patients (12%) and consisted of intense/annoying nonspecific symptoms, persistent PFP, or remaining pareses that influenced functioning. Among the baseline characteristics, 8 of 9 patients with unfavorable outcome were female. Patient sex

Table 3. Cerebrospinal Fluid Findings, Serology, and *Borrelia burgdorferi* Sensu Lato Culture Results in Patients With Bannwarth Syndrome

	Enrollment (n = 77)		3-mo Follow-up (n = 73)	
Laboratory/Culture Finding	Median (IQR) or No. (%) of Patients	95% CI for % or Median	Median (IQR) or No. (%) of Patients	95% CI for % or Median
CSF				
WBC count, $\times 10^6$ cells/L[a]	118[b] (53–299)	117–236	6 (2–10)	5.5–7.5
Elevated (>5 × 10^6 cells/L)	77 (100%)	95.3%–100%	39 (53.4%)	41.4%–65.2%
Elevated (>10 × 10^6 cells/L)	72 (93.5%)	85.5%–97.9%	17 (23.3%)	14.2%–34.6%
% of lymphocytes	92.7 (86.3–95.9)	89.1–93.1	100 (100–100)	100–100
Protein concentration, g/L	0.96 (0.53–1.72)	.93–1.38	0.48 (0.37–0.56)	.44–.52
Elevated (>0.45 g/L)	63 (81.8%)	71.4%–89.7%	42 (57.5%)	45.4%–69.0%
Glucose concentration, mmol/L	2.8 (2.5–3.2)	2.7–3.0	3.0 (2.7–3.3)	2.9–3.1
CSFglu/Sglu <1/3	4 (5.2%)	1.4%–12.8%	2 (2.7%)	.3%–9.5%
Albumin quotient[c]	0.014 (0.008–0.023)	.010–.015	0.007 (0.005–0.009)	.006–.007
Elevated (>0.0074)	66 (85.7%)	75.9%–92.6%	31 (42.5%)	31.0%–54.6%
IgG quotient[c]	0.010 (0.004–0.024)	.008–.014	0.004 (0.003–0.005)	.004–.005
Elevated (>0.0035)	66 (85.7%)	75.9%–92.6%	43 (58.9%)	46.8%–70.3%
Borrelial serology (LIAISON)				
Positive serum IgM	36/59 (61.0%)	47.4%–73.4%	26/65 (40.0%)	28.0%–52.9%
Positive serum IgG	57/59 (96.6%)	88.3%–99.6%	57/65 (87.7%)	77.2%–94.5%
Positive serum IgM and/or IgG	57/59 (96.6%)	88.3%–99.6%	59/65 (90.8%)	81.0%–96.5%
Positive CSF IgM	37/55 (67.3%)	53.3%–79.3%	35/67 (52.2%)	39.7%–64.6%
Positive CSF IgG	50/55 (90.9%)	80.0%–97.0%	59/67 (88.1%)	77.8%–94.7%
Positive CSF IgM and/or IgG	51/55 (92.7%)	82.4%–98.0%	61/67 (91.0%)	81.5%–96.6%
Intrathecal synthesis of specific antibodies present				
IgM Reiber	34/54 (63.0%)	48.7%–75.7%	35/63 (55.5%)	42.5%–68.1%
IgG Reiber	47/53 (88.7%)[d]	77.0%–95.7%	54/63 (85.7%)	74.6%–93.2%
IgM and/or IgG Reiber	49/54 (90.7%)[d]	79.7%–96.9%	57/63 (90.5%)	80.4%–96.4%
Borrelia culture results				
Positive CSF culture	12[e]/77 (15.6%)	8.3%–25.6%	0/73	0%–4.9%
Positive blood culture	2[f]/75 (2.7%)	.3%–9.3%	0/2[g]	0%–84.2%
Positive skin culture	13[h]/32 (40.6%)	23.7%–59.4%	0/13[i]	0%–24.7%

Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid; CSFglu/Sglu, ratio between CSF and serum glucose concentrations; IgG, immunoglobulin G; IgM, immunoglobulin M; IQR, interquartile range; WBC, white blood cell.

[a] In traumatic lumbar puncture, the WBC count was adjusted: for every 1000 × 10^6 red cells/L, 1 × 10^6 white cells/L was subtracted.

[b] Two patients had concomitant tick-borne encephalitis virus infection: 1 showed intrathecal synthesis of borrelial IgM and IgG antibodies; in the other *Borrelia afzelii* was isolated from CSF and blood samples.

[c] Albumin (IgG) quotient is a quotient between CSF and serum albumin (IgG) concentration.

[d] In some patients, intrathecal synthesis of borrelial IgG antibodies could have resulted from a previous borrelial infection (previous Lyme borreliosis of unknown manifestation had been reported in 6 patients).

[e] CSF cultures were positive in 11 of 59 (18.6%) patients who had not received antibiotics and in 1 of 18 (5.5%) patients who had been treated with antibiotics before CSF examination ($P = .275$); the patient with borreliae isolated from CSF had received azithromycin (3 g). Eleven CSF isolates were identified as *Borrelia garinii*, 1 as *B. afzelii*.

[f] Blood cultures were positive in 2 of 58 (3.4%) patients who had not received antibiotics and from 0 of 17 patients who had received antibiotics before examination ($P = 1.0$). Both blood isolates were identified as *B. afzelii*.

[g] Follow-up blood cultures were obtained from 2 patients who had positive pretreatment blood cultures.

[h] Skin samples were cultured from 32 patients: in 20 patients from the actual EM skin lesion and in 12 from the site of past EM; cultures were positive in 10 of 20 (50%) and 3 of 12 (25%) patients, respectively. Borreliae were cultured from skin samples of 11 of 23 (47.8%) patients without previous antibiotic treatment: 9 of 18 (50%) with EM and 2 of 5 (40%) with past EM; similarly from 2 of 9 (22.2%) patients who had received antibiotic therapy before the skin biopsy was collected: 1 patient who had received nitrofurantoin (it has no in vitro efficacy against *Borrelia burgdorferi* sensu lato) and 1 of 8 patients treated with azithromycin. All skin isolates were identified as *B. garinii*.

[i] Skin biopsies were collected only from patients with positive skin culture results at the first visit; the procedure was done at the site of previous biopsy.

was the only characteristic that appeared to be associated with outcome in the univariate analyses. The presence of individual symptoms at enrollment was generally associated with higher probability of unfavorable outcome, but the associations were not statistically significant. However, associations between symptoms at 14 days after enrollment and outcome were significant, and remained strong when penalized ridge regression was used (Supplementary Figure 2). The cross-validated predictive accuracy of the predictive model was excellent (AUC = 0.96), indicating that it is feasible to accurately predict which patients will have an unfavorable outcome 6 or 12 months after treatment, based on the data available in the first 2 weeks. Most of the predictive information was provided by the symptoms at 14 days (Supplementary Figure 3).

DISCUSSION

BS is a typical form of early European LNB, characterized by painful radiculitis and lymphocytic pleocytosis. It is sometimes

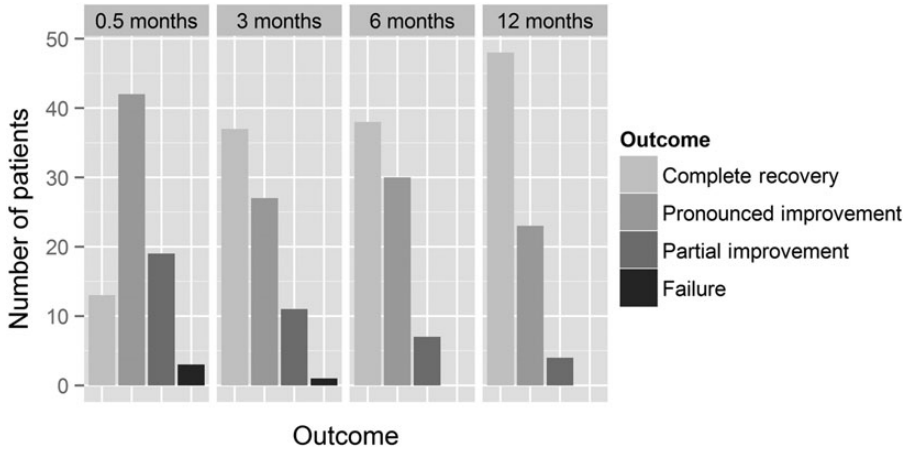

Figure 1. Improvement after antibiotic therapy at 2 weeks, and at 3-, 6-, and 12-month follow-up visits as reported by patients with Bannwarth syndrome (comparison with the pretreatment condition). Three of 77 patients were treated with oral doxycycline, the others with intravenous ceftriaxone. Two patients who received doxycycline recovered completely and the third improved pronouncedly.

accompanied by cranial nerve involvement (usually PFP) that typically appears days to weeks after the beginning of pain. The borrelial etiology is further substantiated by the presence of EM and is proven by demonstration of intrathecal synthesis of borrelial antibodies and/or by evidence of *B. burgdorferi* sensu lato in CSF.

Of the 77 patients included in the present study, 17 (22.1%) had received antibiotic treatment before examination at our institution: 15 patients were treated for EM (13 with azithromycin, 1 with azithromycin plus amoxicillin, 1 with unknown antibiotic); 2 patients were treated for suspected pyelonephritis because of lumbar pain (with ciprofloxacin and nitrofurantoin, respectively). The probable reason for development of LNB despite antibiotic therapy was that these antibiotics were inappropriate for borrelial infection [1].

Comparison of findings in the present study with published results [1, 4, 11, 13, 28] shows that our patients were older (70% were >50 years of age; 34% were 61–70 years) and were more often female. The explanation for higher age could be that, in comparison with younger age groups, older persons have more limited knowledge about LB and lesser ability to recognize EM; consequently, they less often receive appropriate and prompt treatment for EM and more often develop LNB.

More than half of our patients (46/77 [59.7%]) had EM in the course of the disease. At enrollment, EM was still visible (median diameter 35 cm) in 22 of 46 (47.8%) patients. The large diameter corroborates previous European findings [29] and is most likely related to the etiologic agent of LNB, *B. garinii*, which has been associated with faster spread of EM than when caused by other species of borreliae [29, 30].

All our patients reported radicular pain, which was located at the site of present or past EM in 33 of 46 (71.7%) patients with the skin lesion. According to several [6, 8, 9, 10, 12] but not all [13] studies, pain is often localized in the region of a tick bite and/or EM, suggesting that in BS the spirochetes infect peripheral nerves in the vicinity of the bite and then spread centripetally to the central nervous system. This concept is further supported by the observation that patients who were bitten on the head or neck more often had neurologic manifestations of LB than those with tick bites at other locations (20% vs 7%; $P = .005$) [31]. However, in the present study, EM was located on the head/neck in only 1 of 46 (2%) patients with EM in the course of the disease, and her pain was not located in the region of the skin lesion. The statistical analysis showed a significant difference in the distribution of the EM site and location of radicular pain, despite the high proportion of matching locations (Table 2), and was mostly due to the large proportion of patients experiencing radicular pain on the trunk.

In our patients, the median duration of illness before diagnosis was 30 (interquartile range, 14–60) days, and in 12 of 77 patients (15.6%) it was >2 months. Considering the severe pain and usually multiple visits to doctors, this duration of illness is much too long, although still substantially shorter than in older reports where time from the beginning of illness to the diagnosis was usually several months [13, 18]. The shorter duration of neurological symptoms before treatment probably explains the much lower frequency of PFP and pareses in our patients (36.4% and 7.8%, respectively) than in series of patients reported decades ago (60%–89% and 33%–53%, respectively) [4, 13, 18, 32, 33]. Nevertheless, in none of our patients PFP or pareses preceded the onset of radicular pain (it was always vice versa), a finding that corroborates previous reports. Meningeal signs, fever, and vomiting were rare in our patients: they were present in only 19.5%, 19.5%, and 3.9%, respectively. These frequencies are even lower than reported for adult patients with early LNB [3, 28, 29, 34, 35].

Table 4. Presence and Intensity of Symptoms at Enrollment and at Follow-up in Patients With Bannwarth Syndrome

Symptom	Enrollment (N = 77)	Follow-up Visit			
		14 d (n = 77)	3 mo (n = 76)	6 mo[a] (n = 75)	12 mo[a] (n = 75)
Radicular pain					
Present[b]	100	37.7 (26.9–49.4)	10.5 (4.7–19.7)	6.7 (2.2–14.9)	8.0 (3.0–16.6)
Intensity[c]	9 (7–10)	4 (3–5)	6.5 (3–7)	4 (4–5)	3 (3–5)
Sleep disturbances					
Present[b]	75.3 (64.2–84.4)	11.7 (5.5–21.0)	3.9 (0.8–11.1)	5.3 (1.5–13.1)	6.7 (2.2–14.9)
Intensity[c]	9 (8–10)	6 (5–7)	5 (3–5)	5 (3–5)	4 (3–5)
Headache					
Present[b]	46.8 (35.3–58.5)	31.2 (21.1–42.7)	17.1 (9.4–27.5)	25.3 (16.0–36.7)	20.0 (11.6–30.8)
Intensity[c]	6 (4–8)	4 (3–5.5)	3 (2–4)	4.5 (3–5)	5 (4–6)
Fatigue					
Present[b]	44.2 (32.8–55.9)	44.2 (32.8–55.9)	13.2 (6.5–22.9)	12.0 (5.6–21.6)	16.0 (8.5–26.3)
Intensity[c]	6 (4–8)	5 (3–6)	4.5 (3–6)	5 (5–6)	4 (3–6)
Malaise					
Present[b]	39.0 (28.0–50.7)	22.1 (13.4–33.0)	6.6 (2.2–14.7)	9.3 (3.8–18.3)	8.0 (3.0–16.6)
Intensity[c]	7 (5–8)	5 (4–6)	5 (3.5–6.5)	5 (4–5)	5 (3–5)
Paresthesias					
Present[b]	32.5 (22.2–44.1)	24.7 (15.6–35.8)	15.8 (8.4–26.0)	12.0 (5.6–21.6)	12.0 (5.6–21.6)
Intensity[c]	5 (3–7.5)	4 (3–5)	4 (3–8)	5 (4–8)	4 (3–4)
Arthralgia					
Present[b]	26.0 (16.6–37.2)	10.4 (4.6–19.4)	14.5 (7.4–24.4)	16.0 (8.5–26.3)	12.0 (5.6–21.6)
Intensity[c]	7 (5–8)	4.5 (4–6)	5 (2–6)	5 (4–8)	4 (3–4)
Myalgia					
Present[b]	26.0 (16.6–37.2)	11.7 (5.5–21)	9.2 (3.8–18.1)	10.7 (4.7–19.9)	6.7 (2.2–14.9)
Intensity[c]	7 (5.5–8)	4 (3–5)	4 (3–5)	3.5 (2.5–6)	6 (4–7)
Fever					
Present[b]	19.5 (11.3–30.1)	2.6 (0.3–9.1)	0 (0–4.7)	0 (0–4.8)	0 (0–4.8)
Intensity[d]	37.8 (37.5–38.3)	37.3 (37.2–37.5)			
Vertigo					
Present[b]	19.5 (11.3–30.1)	11.7 (5.5–21.0)	9.2 (3.8–18.1)	8.0 (3.0–16.6)	5.3 (1.5–13.1)
Intensity[c]	5 (3–7)	4 (3–6.5)	5.5 (4–8)	4 (2–5)	5 (1–8)
Concentration disturbances					
Present[b]	16.9 (9.3–27.1)	15.6 (8.3–25.6)	11.8 (5.6–21.3)	10.7 (4.7–19.9)	6.7 (2.2–14.9)
Intensity[c]	5 (3–5)	4.5 (3–5)	4.5 (3–5)	4.5 (2.5–5)	4 (3–5)
Memory disturbances					
Present[b]	15.6 (8.3–25.6)	18.2 (10.3–28.6)	13.2 (6.5–22.9)	10.7 (4.7–19.9)	9.3 (3.8–18.3)
Intensity[c]	4.5 (3–5)	3.5 (3–5)	4.5 (2.5–6)	5 (2–5)	5 (3–5)
Nausea					
Present[b]	10.4 (4.6–19.4)	5.2 (1.4–12.8)	5.3 (1.4–12.9)	2.7 (0.3–9.3)	2.7 (0.3–9.3)
Intensity[c]	3 (2–5)	7 (7–7)	6 (5–8)	3 (3–3)	6.5 (5–8)
Vomiting					
Present[b]	3.9 (0.8–11.0)	1.3 (0–7.0)	0 (0–4.7)	0 (0–4.8)	1.3 (0–7.2)
Intensity[c]	6.5 (3–10)	3[e]			4[e]

[a] In 12 patients, antibiotic therapy was repeated within 3–6 months because of intense, annoying symptoms substantially influencing daily activities. Of these, 5 responded promptly: 2 of 4 with objective signs in addition to symptoms and 3 of 8 who reported solely subjective symptoms.

[b] Data are given as percentage (95% confidence interval) of patients with individual symptoms that had newly developed or intensified since the beginning of the current illness and had no other obvious explanation.

[c] Data on intensity of each individual symptom (in patients with the symptom) are expressed as median (interquartile range). The intensity of the present symptom was scored on a scale from 1 to 10.

[d] The intensity of fever is expressed in degrees Celsius as median (interquartile range).

[e] No confidence interval is given because only 1 patient reported the symptom.

More than 96% of our patients with BS had detectable serum borrelial IgG antibodies; in the remaining patients the antibodies were either present only in CSF or completely absent (see Supplementary Material). Intrathecal synthesis of borrelial IgM and IgG antibodies was present in 63% and 89% of the patients, respectively (Table 3). Although these findings are within the (upper) range of published results [5, 6, 12, 14, 18, 29, 36, 37], 9% of patients with BS had no intrathecal synthesis of borrelial

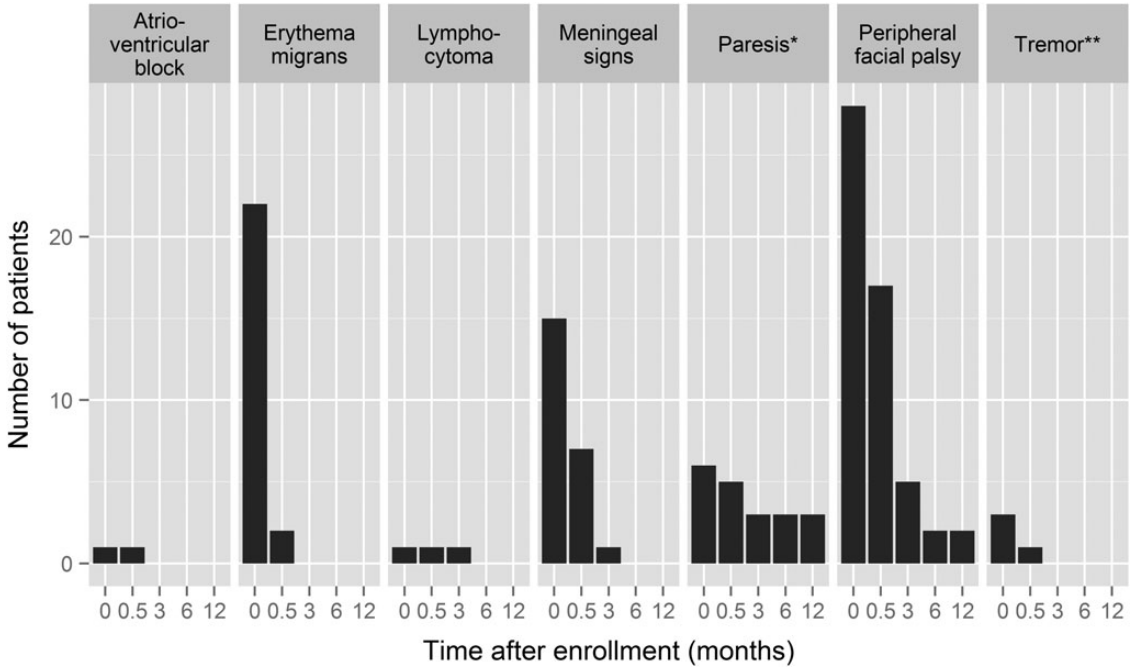

Figure 2. Presence of clinical signs at enrollment and at follow-up visits in patients with Bannwarth syndrome. *All patients tested negative for antibodies to tick-borne encephalitis virus in serum. **One of 3 patients with tremor at enrollment had concomitant tick-borne encephalitis.

antibodies. It was unexpected that patients with (n = 47) or without (n = 6) intrathecal synthesis of borrelial IgG antibodies did not differ in duration of the illness (median 30 vs 35 days; $P = .78$) or in receiving antibiotic treatment before enrollment (25% vs 0%; $P = .32$). However, as not all patients were tested, the number of patients was rather small. During the initial part of the 8-year study, an immunofluorescence test was routinely in use at our institution. For the study, we tested all available serum and CSF samples with an indirect chemiluminescence immunoassay test, but unfortunately specimens were not available from every patient, which is a limitation of our findings.

There were no major surprises in relation to the results of culture for borreliae. The bacteria were isolated from CSF in 12 of 77 (15.6%) patients, which is in the upper range of published isolation rates from CSF in patients with early LNB [11, 28, 29, 38]. The large majority (11/12) of CSF isolates and all 13 skin isolates (10 from the site of present EM, 3 from the site of past EM) were typed as *B. garinii* (Table 3). The results corroborate previous findings identifying *B. garinii* as the principal causative agent of LNB in Europe [28, 29], but are in contrast to an earlier finding that ≥80% of EM skin lesions in Slovenia were caused by *B. afzelii* [22].

The outcome after antibiotic treatment was favorable in the large majority (65/74 [87.8%]) of our patients. EM disappeared during antibiotic treatment in all but 2 patients, in whom it completely vanished soon after the end of therapy. PFP improved more slowly than EM but eventually disappeared in all but 2 (2/28 [7.1%]) patients. Among other objective signs, pareses remained permanent in 3 (3/6 [50%]) patients, but were functionally important in only 1 of them, while all other clinical signs were gone (Figure 2). In addition, the frequency and intensity of the associated symptoms substantially diminished in the majority of patients during 1 year of follow-up (Table 4).

Our model, based on the data available in the first 2 weeks after diagnosis, accurately predicted the patients who would experience an unfavorable outcome 6 or 12 months after treatment (Supplementary Figure 3). Among pretreatment characteristics, only female sex was strongly associated with unfavorable outcome. Most of the predictive information was provided by the symptoms at 14 days: these included nausea, vomiting, memory and concentration disturbances, malaise, fatigue, headache, and arthralgia (Supplementary Figure 2). Data on risk factors for unfavorable outcome in patients with LNB are scarce, and we were not able to find corresponding information specifically for patients with BS. Studies from Norway in patients with definite or possible LNB revealed that more complaints remained 1 year after treatment in the patients with pretreatment duration of symptoms ≥6 weeks, high pretreatment CSF cell count, and female sex [39]; at 30 months after treatment, poorer outcome was recorded in patients with pretreatment symptom duration >6 weeks, more numerous symptoms and findings before treatment, and noncomplete recovery at 4 months [40].

In conclusion, our findings have (1) corroborated previous information on the clinical characteristics of BS, with the exception that our patients were older, more often female, and had

fewer neurological complications (PFP, pareses) than reported decades ago, probably as the result of earlier recognition of the disease; (2) confirmed favorable outcome after a 14-day regimen of antibiotic therapy; (3) demonstrated that it is feasible to accurately predict which patients will experience unfavorable outcome 6 or 12 months after treatment, based on the data available in the first 2 weeks (most of the predictive information was provided by the symptoms at 14 days); and (4) enabled assessment of the value of borrelial culture and assay of intrathecal synthesis of specific antibodies in diagnosis of LNB.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

Disclaimer. The funding source had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Financial support. This work was supported by the Slovenian Research Agency (grant number P3-0296).

Potential conflicts of interest. F. S. had served as a consultant to Baxter regarding Lyme vaccine and is a member of the steering committee of the European Society of Clinical Microbiology and Infectious Diseases Study Group for Lyme Borreliosis. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Stanek G, Wormser GP, Gray J, Strle F. Lyme borreliosis. Lancet **2012**; 379:461–73.
2. Bannwarth A. Chronic lymphocytic meningitis, inflammatory polyneuritis and rheumatism [in German]. Arch Psychiatr Nervenkr **1941**; 113:284–376.
3. Pfister HW, Kristoferitsch W, Meier C. Early neurologic involvement (Bannwarth's syndrome). In: Weber K, Burgdorfer W, eds. Aspects of Lyme borreliosis. Berlin, Germany: Springer-Verlag, **1993**; 152–67.
4. Schmidt R, Ackermann R. Meningopolyneuritis (Garin-Bujadoux, Bannwarth) erythema chronicum migrans disease of the nervous system transmitted by ticks [in German]. Fortschr Neurol Psychiatr **1985**; 53:145–53.
5. Stiernstedt G, Sköldenberg B, Gårde A, et al. Clinical manifestations of *Borrelia* infections of the nervous system. Zentralbl Bakteriol Mikrobiol Hyg A **1987**; 263:289–96.
6. Pfister HW, Einhäupl KM, Wilske B, Preac-Mursic V. Bannwarth's syndrome and the enlarged neurological spectrum of arthropod-borne borreliosis. Zenralbl Bakteriol Mikrobiol Hyg A **1987**; 263:343–7.
7. Kristoferitsch W. Neuropathies in lyme borreliosis [in German]. New York: Springer, **1989**.
8. Garin C, Bujadoux C. Paralysis by ticks [in French]. J Med Lyon **1922**; 71:765–7.
9. Schaltenbrand G. Radiculomyelomeningitis after tick bite [in German]. Münch Med Wschr **1962**; 18:829–34.
10. Bammer H, Schenk K. Meningo-Myelo-Radiculitis after a tick bite with Erythema [in German]. Dtsch Z Nervenheilkd **1965**; 187:25–34.
11. Roux F, Boyer E, Jaulhac B, Dernis E, Closs-Prophette F, Puéchal X. Lyme meningoradiculitis: prospective evaluation of biological diagnosis methods. Eur J Clin Microbiol Infect Dis **2007**; 26:685–93.
12. Dupuis M, Mertens C, Gonsette RE, Nuytten W, Bouffioux J, Dobbelaere F. Meningoradiculitis caused by a spirochete (*Borrelia burgdorferi*) after arthropod bite [in French]. Rev Neurol (Paris) **1985**; 141:780–5.
13. Ackermann R, Hörstrup P, Schmidt R. Tick-borne meningopolyneuritis (Garin-Bujadoux, Bannwarth). Yale J Biol Med **1984**; 57:485–90.
14. Kohler J, Thoden U. Pain syndromes in tick-borne neuroborreliosis. Clinical aspects and differential diagnosis [in German]. Schmerz **1987**; 1:107–13.
15. Viader F, Poncelet AM, Chapon F, et al. Neurologic forms of Lyme disease. 12 cases [in French]. Rev Neurol (Paris) **1989**; 145:362–8.
16. Kristoferitsch W, Baumhackl U, Sluga E, Stanek G, Zeiler K. High-dose penicillin therapy in meningopolyneuritis Garin-Bujadoux-Bannwarth. Clinical and cerebrospinal fluid data. Zentralbl Bakteriol Mikrobiol Hyg A **1987**; 263:357–64.
17. Hirsch E, Sellal F, Christmann D, et al. Meningoradiculitis after a tick bite. Study of 31 cases [in French]. Rev Neurol (Paris) **1987**; 143:182–8.
18. Ryberg B. Bannwarth's syndrome (lymphocytic meningoradiculitis) in Sweden. Yale J Biol Med **1984**; 57:499–503.
19. Pachner AR, Steere AC. The triad of neurologic manifestation of Lyme disease: meningitis, cranial neuritis and radiculoneuritis. Neurology **1985**; 35:47–53.
20. Stanek G, Fingerle V, Hunfeld KP, et al. Lyme borreliosis: clinical case definitions for diagnosis and management in Europe. Clin Microbiol Infect **2011**; 17:69–79.
21. Reiber H, Peter JB. Cerebrospinal fluid analysis: disease-related data patterns and evaluation programs. J Neurol Sci **2001**; 184:101–22.
22. Ružić-Sabljić E, Maraspin V, Lotrič-Furlan S, et al. Characterization of *Borrelia burgdorferi* sensu lato strains isolated from human material in Slovenia. Wien Klin Wochenschr **2002**; 114:544–50.
23. Ružić-Sabljić E, Zore A, Strle F. Characterization of *Borrelia burgdorferi* sensu lato isolates by pulsed-field gel electrophoresis after MluI restriction of genomic DNA. Res Microbiol **2008**; 159:441–8.
24. Postic D, Assous MV, Grimont PAV, Baranton G. Diversity of *Borrelia burgdorferi* sensu lato evidenced by restriction fragment length polymorphism of rrf (5S)–rrl (23S) intergenic spacer amplicons. Int J Syst Bacteriol **1994**; 44:743–52.
25. Heinze G, Schemper M. A solution to the problem of separation in logistic regression. Statist Med **2002**; 21:2409–19.
26. R Core Team 2015 R. A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing. Available at: http://www.r-project.org/. Accessed 12 October 2015.
27. Friedman J, Hastie T, Tibshirani R. Regularization paths for generalized linear models via coordinate descent. J Stat Softw **2010**; 33:1–22.
28. Strle F, Ruzić-Sabljić E, Cimperman J, Lotrič-Furlan S, Maraspin V. Comparison of findings for patients with *Borrelia garinii* and *Borrelia afzelii* isolated from cerebrospinal fluid. Clin Infect Dis **2006**; 43:704–10.
29. Ogrinc K, Lotrič-Furlan S, Maraspin V, et al. Suspected early Lyme neuroborreliosis in patients with erythema migrans. Clin Infect Dis **2013**; 57:501–9.
30. Strle F, Ružić-Sabljić E, Logar M, et al. Comparison of erythema migrans caused by *Borrelia burgdorferi* and *Borrelia garinii*. Vector Borne Zoonotic Dis **2011**; 11:1253–8.
31. Berglund J, Eitrem R, Ornstein K, et al. An epidemiologic study of Lyme disease in southern Sweden. New Engl J Med **1995**; 333:1319–24.
32. Roloff A, Laskawi R, Argyrakis A. Differential diagnosis of idiopathic facial paralysis: Bannwarth meningopolyradiculitis [in German]. HNO **1986**; 34:149–50.
33. Laubert A, Malin JP. Prognosis of peripheral facial paralysis in Lyme borreliosis (Garin-Bujadoux, Bannwarth meningopolyradiculitis) [in German]. HNO **1989**; 37:158–61.
34. Borg R, Dotevall L, Hagberg L, et al. Intravenous ceftriaxone compared with oral doxycycline for the treatment of Lyme neuroborreliosis. Scand J Infect Dis **2005**; 37:449–54.
35. Ljøstad U, Skogvoll E, Eikeland R, et al. Oral doxycycline versus intravenous ceftriaxone for European Lyme neuroborreliosis: a multicentre, non-inferiority, double-blind, randomised trial. Lancet Neurol **2008**; 7:690–5.
36. Wilske B, Schierz G, Preac-Mursic V, et al. Intrathecal production of specific antibodies against *Borrelia burgdorferi* in patients with lymphocytic meningoradiculitis (Bannwarth's syndrome). J Infect Dis **1986**; 153:304–14.
37. Hansen K, Lebech AM. Lyme neuroborreliosis: a new sensitive diagnostic assay for intrathecal synthesis of *Borrelia burgdorferi*-specific immunoglobulin G, A, and M. Ann Neurol **1991**; 30:197–205.
38. Karlsson M, Hovind-Hougen K, Svenungsson B, Stiernstedt G. Cultivation and characterization of spirochetes from cerebrospinal fluid of patients with Lyme borreliosis. J Clin Microbiol **1990**; 28:473–9.
39. Ljøstad U, Mygland Å. Remaining complaints 1 year after treatment for acute Lyme neuroborreliosis; frequency, pattern and risk factors. Eur J Neurol **2010**; 17:118–23.
40. Eikeland R, Mygland Å, Herlofson K, Ljøstad U. Risk factors for a non-favorable outcome after treated European neuroborreliosis. Acta Neurol Scand **2013**; 127:154–60.