

Colocalization of Radicular Pain and Erythema Migrans in Patients With Bannwarth Syndrome Suggests a Direct Spread of *Borrelia* Into the Central Nervous System

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Background. There is a general assumption that after deposition into skin, Lyme borreliae disseminate hematogenously to other organs, resulting in extracutaneous manifestations of Lyme borreliosis, including Lyme neuroborreliosis. However, our experience over the past 40 years, along with several published case reports that observed colocalization of radicular pain and erythema migrans (EM) in patients with borrelial meningoradiculoneuritis (Bannwarth syndrome), argues against hematogenous dissemination in Lyme neuroborreliosis.

Methods. We compared the location of EM in 112 patients with Bannwarth syndrome to 12 315 EM patients without neurological involvement. Moreover, we assessed the colocalization of EM and radicular pain in patients with Bannwarth syndrome.

Results. Compared to >12 000 EM patients without neurological involvement, patients with Bannwarth syndrome had a significantly higher frequency of EM on head/neck (6% vs 1%; $P = .0005$) and trunk (47% vs 24%; $P < .0001$), similar frequency on arms (16% vs 16%; $P = .91$), but lower frequency on legs (30% vs 59%; $P < .0001$). Moreover, in 79% (89/112) of patients the site of EM matched the dermatomes of radicular pain. The odds for a congruent location of EM and radicular pain were highly significant with the highest odds ratios (OR) observed for head (OR = 221), followed by neck (OR = 159), legs (OR = 69), arms (OR = 48), and trunk (OR = 33).

Conclusions. The greater frequency of EM on head/neck and trunk and the colocalization of EM with radicular pain in patients with Bannwarth syndrome suggest that central nervous system involvement in Lyme neuroborreliosis is due to a retrograde spread of borrelia from skin to the spinal cord via peripheral nerves.

Keywords. Lyme neuroborreliosis; Bannwarth syndrome; erythema migrans; radicular pain; *B. garinii*.

Lyme borreliosis (LB) is the most common tick-transmitted disease in the northern hemisphere. In Europe the majority of cases are due to infection with *Borrelia afzelii* and *Borrelia garinii*, whereas in North America, LB is nearly exclusively caused by *Borrelia burgdorferi*. Differences in the distribution of these etiologic agents are likely a key reason for the variation in the clinical presentation of LB in North America and Europe. Indeed, *B. afzelii* has the greatest propensity to cause skin manifestations, *B. garinii* is the main cause of central nervous system (CNS) involvement, whereas infection with *B. burgdorferi* often

leads to arthritis [1–3]. With all 3 species, the first sign of infection is usually an erythema migrans (EM) skin lesion that develops within days to a few weeks at the site of tick bite and inoculation of *B. burgdorferi* sensu lato (Lyme borrelia) into skin. In untreated individuals, the causative agent may disseminate, presumably hematogenously, to affect other organs and tissues, resulting in secondary skin lesions (multiple EM) and/or involvement of the CNS, heart, or joints [1–3].

In Europe, Lyme neuroborreliosis (LNB) is the second most common clinical manifestation of disseminated LB (after multiple EM). Bannwarth syndrome, a painful meningoradiculoneuritis, is the most typical LNB manifestation in adults [4, 5]. Almost 60% of patients with Bannwarth syndrome have EM before the onset of neurological involvement [5].

Epidemiological data from Sweden suggest that tick bites on the head are more often associated with LNB than bites at other locations [6]. Furthermore, based on several early case reports or small series ($N \leq 10$) of patients with Bannwarth syndrome, there is an impression that radicular pain often occurs at the site of (previous) EM [7–17]. If true, these observations argue

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against hematogenous dissemination of Lyme borreliae as the explanation for CNS involvement in LNB. Instead, they suggest that the spirochetes spread from the site of primary infection in the skin to the nerves and then centripetally along the nerves toward the CNS.

In this study we challenged the current dogma that LNB, and more specifically Bannwarth syndrome, is the result of hematogenous dissemination of borreliae to CNS using a cohort of >12 400 EM patients, including 112 with Bannwarth syndrome.

METHODS

Patients

This study is based on clinical information from >12 400 adult EM patients diagnosed and evaluated at our LB Outpatient Clinic: 12 315 without neurological impairment, seen in the period 1990–2014, and 112 with Bannwarth syndrome with accompanying EM, seen from 2006 to 2020. In this time period, a total of 187 patients with Bannwarth syndrome were evaluated at our institution of whom 75 were without EM.

We tested 2 primary hypotheses:

1. The location of EM in patients with Bannwarth syndrome differs from that in LB patients without neurological impairment.

To test this hypothesis, we compared the body location of EM in 12 315 patients without neurological impairment and in 112 patients with Bannwarth syndrome, all of whom were diagnosed at the same clinic. Four basic locations were delineated: head and neck, trunk, arm (including axillary and shoulder region), and leg (including inguinal and gluteal region). In patients with multiple EM, the location of primary EM was used.

2. In patients with Bannwarth syndrome, EM localizes to the site of radicular pain.

To test this hypothesis, we compared the location of EM and radicular pain in 112 patients with Bannwarth syndrome, with the assumption that colocalization of EM and radicular pain favors “per continuitatem” (nonsystemic) spread of *Borrelia* and against hematogenous dissemination. In patients with multiple EM, the location of primary EM was used. Colocalization was present when EM and radicular pain occurred in the same dermatomes on the same body side.

Definitions

EM was defined as an expanding erythematous skin lesion, with or without central clearing, that developed days to weeks after a tick bite or exposure to ticks in an LB endemic region and had a diameter ≥ 5 cm. If < 5 cm in diameter, a history of tick bite, a delay in the appearance of at least 2 days, and an expanding rash at the bite site were required for diagnosis of EM [2].

Multiple EM was defined as the presence of ≥ 2 skin lesions, at least 1 of which fulfilled the size criteria (≥ 5 cm) for solitary EM. The EM that appeared at the site of the tick bite was defined as the primary EM. If no tick bite was recalled, the primary EM was defined as the lesion with longest duration, or in the case of the same or uncertain duration, the 1 with the largest diameter.

Bannwarth syndrome (borreliar meningoradiculoneuritis) was defined based on presence of 3 criteria: (1) radicular pain (very intense pain that typically worsens at night and doesn't respond well to usual analgesics), (2) lymphocytic pleocytosis ($> 5 \times 10^6$ leukocytes/L) in the cerebrospinal fluid (CSF), and (3) demonstration of borreliar CNS infection by intrathecal synthesis of borreliar antibodies and/or isolation of borrelia from CSF. Only the subset of patients with Bannwarth syndrome who had EM qualified for the present study.

Serological Evaluation

Antibodies to Lyme borrelia in serum and CSF were determined using indirect chemiluminescence immunoassay with recombinant outer surface protein C (OspC) and Vmp-like sequence, Expressed (VlsE) for detection of immunoglobulin M (IgM), and VlsE for immunoglobulin G (IgG) (LIAISON, Diasorin, Italy). Intrathecal borreliar antibody synthesis was determined as described by Reiber and Peter: antibody index > 1.4 was indicative of intrathecal borreliar antibody production [18].

Cultivation and Typing of *B. burgdorferi* Sensu Lato

Cultivation of borreliae was performed in patients with Bannwarth syndrome from various sites: CSF (all 112 patients), EM skin (70 patients), and blood (105 patients), as described previously [19]. CSF (1 mL) and skin (3 mm EM punch biopsies) were inoculated directly into tubes containing 7 mL modified Kelly-Petternkofer (MKP) medium. Blood samples were centrifuged, and 1 mL of plasma was 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 for up to 12 weeks. PCR-based restriction fragment-length polymorphism or *MluI* restriction of genomic DNA followed by pulsed-field gel electrophoresis were used for species/strain determinations [20, 21].

Statistical Analysis

Continuous variables were summarized using median values and interquartile ranges (IQRs) and discrete variables using counts and percentages (with 95% confidence intervals [CIs]). For discrete variables, all comparisons between groups were based on a Fisher exact test. *P* values $< .05$ were considered statistically significant. Benjamini-Hochberg test was used to adjust *P* values for multiple comparisons where appropriate.

Co-occurrence analysis was used to assess the frequency of matching locations of EM skin lesion and radicular pain in patients with Bannwarth syndrome. The co-occurrence matrix was

first calculated as the cross product between the set of variables corresponding to location of EM and those related to location of radicular pain. Next, Fisher exact test of independence was used to assess the differences between observed and expected co-occurrence frequencies for all pairs in the co-occurrence matrix. Finally, *P* values were adjusted for multiple comparisons using Benjamini-Hochberg procedure. The effect size for each pair of locations was presented as an odd ratio (OR). In our settings, OR >1 reflects a pair where the observed count is larger than would be expected by chance. Similarly, OR < 1 indicates a pair of locations where the observed frequency is less than expected. ORs were log-transformed for visualization purposes to facilitate evaluation of the practical significance of effect sizes.

All statistical analyses were performed using R software [22].

RESULTS

Of 112 patients with Bannwarth syndrome, 55 (49%) were female and 57 (51%) male, with a median age of 60 (IQR 52–67) years. Seven patients (6%) had multiple EM; others had solitary EM. Duration of EM prior to diagnosis was much longer than in the group without CNS involvement (30 [IQR 10–45] vs 10 [IQR 4–24] days; *P* < .0001).

Borreliae were isolated from CSF in 11/112 (10%) patients, from skin in 24/70 (34%) patients and from blood in only 1 of 105 (1%) patients. All CSF isolates and all but one skin isolates were *B. garinii*. The only blood isolate was *B. afzelii* (Table 1).

Location of EM in Patients With or Without Neurologic Involvement

Comparison of EM characteristics in 112 patients with Bannwarth syndrome and 12 315 EM patients without neurological involvement demonstrated that those with Bannwarth syndrome had a greater frequency of EM on the head/neck (6% vs 1%; *P* = .0005) and trunk (47% vs 24%; *P* < .0001), similar frequency on arms (16% vs 16%; *P* = .91), and lower frequency on the legs (30% vs 59%; *P* < .0001) (Table 2). A similar proportion of multiple EM was observed in both groups (6% in Bannwarth syndrome vs 6% in those without neurological involvement).

Table 1. Isolation of *Borrelia* From Skin, Blood and Cerebrospinal Fluid of Patients With Meningoradiculoneuritis (Bannwarth Syndrome)

Source	Positive Culture Result	Isolated Species	
		<i>B. garinii</i>	<i>B. afzelii</i>
Skin ^a	24 ^b /70 (34%)	23	1
Blood	1 ^c /105 (1%)	0	1
CSF	11 ^d /112 (10%)	11	0

Abbreviation: CSF, cerebrospinal fluid.

^aSkin biopsy was performed at the site of the existent erythema migrans (EM) or at the site of previous (recently disappeared) EM.

^b*Borreliae* were isolated from the border of existing EM (21/55, 38%) or from the normal looking skin at the site of recently disappeared EM skin lesion (3/15, 20%); skin culture was positive in 2/12 (17%) patients who received previous antibiotic therapy and in 22/58 (38%) without antecedent antibiotics.

^cBlood culture was positive in 0/38 patients who received previous antibiotic therapy and in 1/67 (1%) without antecedent antibiotics.

^dCSF culture was positive in 2/38 (5%) patients who received previous antibiotic therapy and in 9/74 (12%) without antecedent antibiotics.

Colocalization of EM With Radicular Pain in Patients With Bannwarth Syndrome

The dermatomes of EM and radicular pain matched in 89/112 (79%) patients with Bannwarth syndrome (Figure 1A, Table 3). The chances for a congruent location of EM and radicular pain were much higher than expected to happen by chance, with the greatest ORs observed for head (OR = 221) and neck (OR = 159), followed by leg (OR = 69), arm (OR = 48), and trunk (OR = 33). Detailed findings are shown in Figure 1B and Table 4. Patients in whom radicular pain did not colocalize with EM (N = 23/112, 21%) had no higher indications suggestive of systemic dissemination than those with colocalized EM and radicular pain (N = 89, 79%) as the proportion of patients with multiple EM (2/23 [9%] vs 5/89 [6%]; *P* = .44), and the frequency of systemic symptoms (including nausea, vomiting, paresthesias, memory disturbances, concentration disturbances, sleep disturbances, fatigue, headache, myalgia, arthralgia) were similar in both groups. Primary lesion in patients with multiple EM colocalized with radicular pain with similar frequency as found for solitary EM (5/7, 71% vs 84/105, 80%; *P* = .44).

Table 2. Location of Erythema Migrans (EM) in 112 Adult Patients With Bannwarth Syndrome Who Had EM in the Course of the Disease and in 12 315 Patients With EM and No Signs of Lyme Neuroborreliosis

Location of EM	Bannwarth Syndrome (2006–2020)		Patients With No Signs of LNB (1990–2014)		<i>P</i>
	N (%)	95% CI	N (%)	95% CI	
Head/neck	7 (6%)	3–13%	146 (1%)	1–1%	.0005
Trunk	53 (47%)	38–57%	2913 (24%)	23–24%	<.0001
Arm ^a	18 (16%)	10–24%	1974 (16%)	15–17%	.91
Leg ^b	34 (30%)	22–40%	7282 (59%)	58–61%	<.0001
Total	112		12 315		

In patients with multiple EM (N = 7/112 in the group with Bannwarth syndrome; N = 750/12 315 in patients with no LNB) the location of primary EM was considered.

Abbreviations: CI, confidence interval; LNB, Lyme neuroborreliosis.

^aIncluding axillary and shoulder region.

^bIncluding inguinal and gluteal region.

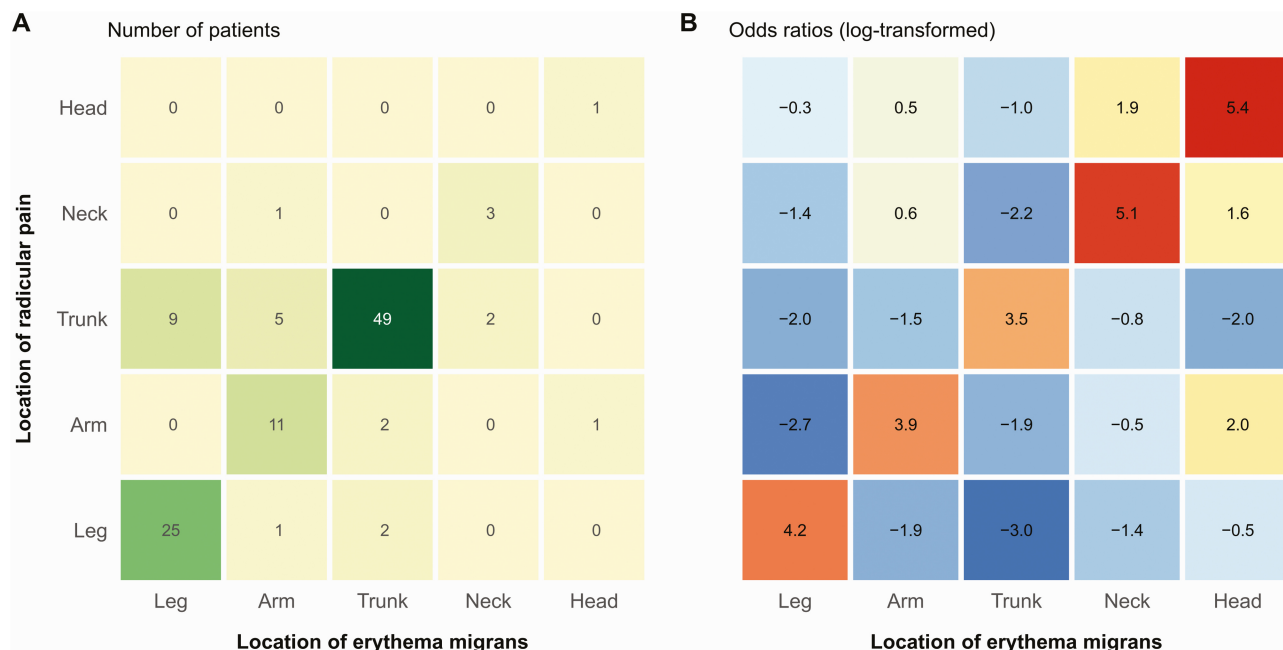


Figure 1. A, Heatmap of observed frequencies for pairs of erythema migrans (EM)-radicular pain (RP) locations. Darker tones correspond to higher counts. B, Heatmap of corresponding ORs evaluating associations between observed and expected frequencies. ORs are shown log-transformed. Red indicates positive effect sizes (ie, observed frequency > expected frequency), whereas blue indicates negative effect sizes (ie, observed frequency < expected frequency). In individuals with correlation between the sites of EM and RP, comparable dermatomes on the same body side were affected. Abbreviation: OR, odds ratio.

DISCUSSION

Slovenia is highly endemic for LB [23, 24]. Over the past 30 years we have recruited and studied a large number of patients with various manifestations of LB, including those with EM, the most common first sign of LB, as well as those with

meningoradiculoneuritis (Bannwarth syndrome). Bannwarth syndrome is the most typical manifestation of early LNB in Europe and is characterized clinically by pronounced radicular pain. This study was possible because of this large collection of samples and clinical information.

Table 3. Location of Radicular Pain (RP) According to Location of the Skin Lesion in 112 Patients With Bannwarth Syndrome Who Had Erythema Migrans (EM) in the Course of the Disease

Location of EM	Location of RP				Total
	Head/neck	Trunk	Arm ^a	Leg ^b	
Head/neck	4 ^c 4/7 (57%) 4/5 (80%)	2 2/7 (29%) 2/65 (3%)	1 1/7 (14%) 1/14 (7%)	0	7 (6%; 3–12%)
Trunk	0	49 ^c 49/53 (92%) 49/65 (75%)	2 2/53 (4%) 2/14 (14%)	2 2/53 (4%) 2/28 (7%)	53 (47%; 38–57%)
Arm ^a	1 1/18 (6%) 1/5 (20%)	5 5/18 (28%) 5/65 (8%)	11 ^c 11/18 (61%) 11/14 (79%)	1 1/18 (6%) 1/28 (4%)	18 (16%; 10–24%)
Leg ^b	0	9 9/34 (27%) 9/65 (14%)	0	25 ^c 25/34 (74%) 25/28 (89%)	34 (30%; 22–40%)
Total	5 (5%; 2–10%)	65 (58%; 48–67%)	14 (13%; 7–20%)	28 (25%; 17–34%)	112

In each box, the 1st row shows the number of patients; the 2nd row shows the percentage of patients with certain RP location for defined EM location; the 3rd row shows the percentage of patients with certain EM location for defined RP location. Data for individual location are reported as number (%), for total as number (%; 95% confidence interval).

In patients with multiple EM (N = 7), the location of primary EM was considered.

^aIncluding axillary and shoulder region.

^bIncluding inguinal and gluteal region.

^cIn individuals with correlation between the sites of EM and RP, comparable dermatomes on the same body side were affected.

Table 4. Frequency Counts and Co-Occurrences Between Erythema Migrans (EM) and Radicular Pain (RP) Locations in 112 Patients With Bannwarth Syndrome

EM Loc	RP Loc	EM Freq	RP Freq	Exp Freq	Coc Freq	P_{adj}	OR	Log (OR)
Head	Head	2	1	0.02	1 ^a	.045	221	5.40
Neck	Neck	5	4	0.18	3 ^a	.001	159	5.07
Trunk	Trunk	53	65	30.76	49 ^a	<.001	33	3.49
Arm	Arm	18	14	2.25	11 ^a	<.001	48	3.86
Leg	Leg	34	28	8.50	25 ^a	<.001	69	4.24
Head	Neck	2	4	0.07	0	>.999	5	1.55
Head	Trunk	2	65	1.16	0	.334	0.14	-1.97
Head	Arm	2	14	0.25	1	.420	7	2.01
Head	Leg	2	28	0.50	0	>.999	0.58	-0.55
Neck	Head	5	1	0.04	0	>.999	6	1.86
Neck	Trunk	5	65	2.90	2	.900	0.47	-0.76
Neck	Arm	5	14	0.63	0	>.999	0.59	-0.53
Neck	Leg	5	28	1.25	0	.514	0.25	-1.37
Trunk	Head	53	1	0.47	0	>.999	0.36	-1.01
Trunk	Neck	53	4	1.89	0	.251	0.12	-2.16
Trunk	Arm	53	14	6.63	2	.026	0.15	-1.87
Trunk	Leg	53	28	13.25	2	<.001	0.05	-3.00
Arm	Head	18	1	0.16	0	>.999	2	0.52
Arm	Neck	18	4	0.64	1	.749	2	0.58
Arm	Trunk	18	65	10.45	5	.024	0.22	-1.52
Arm	Leg	18	28	4.50	1	.091	0.15	-1.92
Leg	Head	34	1	0.30	0	>.999	0.75	-0.29
Leg	Neck	34	4	1.21	0	.514	0.24	-1.43
Leg	Trunk	34	65	19.73	9	<.001	0.14	-1.96
Leg	Arm	34	14	4.25	0	.018	0.06	-2.74

Abbreviations: Coc Freq, observed co-occurrence frequency; EM Freq, number of patients with specific EM location; EM Loc, location of EM; Exp Freq, expected co-occurrence frequency; OR, odds ratio; P_{adj} , adjusted *P* value; RP Freq, number of patients with specific RP location; RP Loc, location of RP.

^aIn individuals with correlation between the sites of EM and RP, comparable dermatomes on the same body side were affected.

Previous epidemiologic observation from Sweden showed that patients with LB who were bitten by ticks on the head or neck had neurological manifestations of LB approximately 3 times more often than those with tick bites at other locations (20% vs 7%; $P = .005$). However, because tick bite does not equate infection or disease, the authors concluded that “it is not clear whether these associations are causal or not, and, if it is causal, neurological manifestations may be caused by a direct invasion of the nervous tissue through blood vessels or neurogenic spread” [6]. In the present study, we expanded on this concept using a large cohort of adult LB patients who fulfilled strict definition criteria for Bannwarth syndrome and/or EM. Based on the assumption that location of the tick bite on head/neck is associated with development of LNB, we postulated that patients with Bannwarth syndrome will have EM more frequently on the head/neck than EM patients without clinical signs of LNB because EM skin lesion develops at the site of the tick bite and inoculation of borreliae into skin. We confirmed this hypothesis by showing that EM on the head/neck was significantly more common in patients with Bannwarth syndrome. However, this comparison also revealed differences in EM location in other body sites: EM

on trunk was significantly more common in patients with Bannwarth syndrome, whereas EM on legs was substantially more frequent in patients without neurological signs than in those with Bannwarth syndrome (59% vs 30%). Interestingly, the frequency of EM on arms was similar in both groups. In adults, EM occurs most frequently on lower extremities presumably because these locations are most exposed to ticks and thus tick bites. In contrast, in patients with Bannwarth syndrome there is a shift toward greater involvement of the torso and the upper body sites (head/neck). We postulate that this is probably due to the greater likelihood that tick bites on the head, neck, or torso lead to CNS involvement, rather than to increased predisposition of LNB patients to tick bites at these sites.

To gain further insights into pathogenesis, we assessed if EM colocalizes with radicular pain in patients with Bannwarth syndrome. Several [7–17] but not all [5, 25, 26] case series and case reports suggest that radicular pain is often localized in the region of a tick bite and/or EM, but this was not assessed thoroughly or in large numbers of patients. In the present study, based on much higher number of patients fulfilling strict definition criteria for Bannwarth syndrome and EM the dermatomes of EM

and radicular pain sites matched in 79%, which was highly significant. The odds for congruent location of radicular pain and EM were the highest for head (OR = 221) and neck (OR = 159), followed by leg (OR = 69), arm (OR = 48) and trunk (OR = 33). The most common location of radicular pain as well as EM was trunk in 65/112 (58%) and 53/112 (47%) patients, respectively.

The greater prevalence of EM on head, neck and torso in patients with Bannwarth syndrome and, in particular, the colocalization of radicular pain and EM in patients with Bannwarth syndrome, suggest that in these patients the spirochetes infect peripheral nerves in the vicinity of the tick bite and then spread centripetally to the CNS, presumably along nerves, rather than systemically through hematogenous dissemination. This concept is further supported by the similar frequency of multiple EM lesions in patients with Bannwarth syndrome (6%) and in those without CNS involvement (6%). If Bannwarth syndrome was due to hematogenous dissemination, one would anticipate a greater frequency of multiple EM lesions as well as symptoms associated with systemic dissemination, but this was not observed. Finally, despite actively searching for the presence of Lyme borrelia, we obtained only 1 positive culture result in blood in 105 patients with Bannwarth syndrome. This isolate was *B. afzelii* that is unusual for patients with Bannwarth syndrome who are typically infected with *B. garinii*. The significance of this result is blunted somewhat by the fact that the frequency of spirochetemia in untreated European patients with EM is exceedingly low (1–8%) [27–31], and several of our patients (38/105 [36%]) received antibiotics prior to blood culturing. Nevertheless, borreliae were concurrently isolated from CSF in 11/112 (10%) of these patients, and all 11 isolates were *B. garinii*. Because PCR did not prove to be additionally beneficial for detection of hematogenous dissemination of borreliae, using only culture was most probably not an important limitation [32].

The presence of EM in a substantial proportion of patients with Bannwarth syndrome, coupled with colocalization of EM with radicular pain, implies a close association of these manifestations. The most plausible explanation for inflammation of the nerve roots within the corresponding dermatome of EM is the spread of borrelia from skin to the local nerves and then centripetally along nerves to nerve roots and the spinal cord. Such retrograde spread of causative agents from the site of inoculation is well recognized in viral infections such as rabies, herpes simplex virus infection, and varicella zoster virus infection [33]. However, this has not been reported previously for bacterial infections with the possible exception of *Listeria monocytogenes* as suggested by in vitro study on rats [34], and the proposed mechanisms for virus spread is hardly applicable for bacteria [35]. It remains unexplained why nerve roots are the main target of infection and thus inflammation in patients with Bannwarth syndrome.

The mechanisms underlying centripetal spread of borrelia along nerves, rather than hematogenously, in Bannwarth

syndrome are not yet known. An intriguing explanation comes from in vitro studies of borrelia complement resistance which show that *B. garinii*, the principal cause of Bannwarth syndrome [5], is more sensitive to human serum than other *Borrelia* genospecies [36, 37]. If true in humans, one would postulate that complement killing in serum would preclude *B. garinii* to disseminate through blood to invade the CNS. In contrast, the relative lack of complement in CSF and in the CNS [38] has been hypothesized as an explanation for the viability of *B. garinii* in the CNS [39, 40]. Our findings are consistent with this concept. Of the 36 *Borrelia* isolates that were cultured from patients with Bannwarth syndrome, 34 were *B. garinii* and all 34 were recovered from CSF or skin, whereas the 2 *B. afzelii* isolates were the only isolate recovered from blood and 1/24 isolates from skin. These results suggest that CSF provides a permissive environment for *B. garinii*, the predominant causative agent of Bannwarth syndrome, whereas blood is cytotoxic to this *Borrelia* species, presumably due to pathogenic host immune responses such as complement-mediated killing.

A key strength of our research approach is the detailed clinical information in a large cohort of well-defined patients with EM including a subset with Bannwarth syndrome. However, a limitation of this cohort is that it is based on adult patients with meningoradiculoneuritis, and thus the findings, although relevant, may not be completely translatable to children or to other LNB manifestations such as peripheral facial palsy without radiculoneuritis. Moreover, it is not yet clear if and how such findings may relate to patients with LNB in North America, where the disease is almost exclusively due to *B. burgdorferi* and meningoradiculoneuritis is rare.

CONCLUSION

Comparison of a large well-defined cohort of EM patients with or without neurological involvement suggests a centripetal spread of borrelia from skin to CNS via peripheral nerves and argues against the established dogma that spirochetes disseminate hematogenously to the CNS. This notion is supported by several findings. First, in patients with Bannwarth syndrome, EM more often occurs on the head, neck, and torso, which is in closer proximity to CNS than the (lower) extremities, which are a far more common site of EM in LB patients without neurological involvement. Second, in 79% of patients with Bannwarth syndrome, EM is localized to the site of radicular pain. Third, 34/36 (94%) of isolates recovered from Bannwarth syndrome patients were *B. garinii*, all of which were recovered from CSF and skin but not blood, consistent with the notion that blood, but not CSF, is toxic to *B. garinii*, the predominant causative agent of Bannwarth syndrome. Although such retrograde spread via nerves is well recognized for viral infections, this is the first such report for a bacterial infection in humans and provides a new paradigm for the study of borrelia dissemination

and CNS involvement in LB. The mechanisms underlying these concepts remain to be established.

Notes

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