

Season is an unreliable predictor of Lyme neuroborreliosis

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ABSTRACT

BACKGROUND: Lyme neuroborreliosis (LNB) is a tick-borne infection of the nervous system caused by the spirochete *Borrelia burgdorferi* sensu lato. The primary symptoms are usually painful radiculitis, facial palsy and lymphocytic meningitis. The aim of this study was to provide data on the seasonal variation, anamnesis, symptoms, laboratory data and course of the disease in adults (≥ 16 years).

METHODS: The medical records of 69 patients with confirmed LNB who attended the Department of Neurology, Lillebaelt Hospital, Vejle, Denmark, were analysed. The diagnosis was confirmed by the presence of leucocytosis in the cerebrospinal fluid and intrathecal production of immunoglobulin M and/or G anti-*B. burgdorferi* antibodies.

RESULTS: Onset of neurological symptoms in LNB occurred year round in the Region of Southern Denmark. Only half of the patients had a history of a tick bite or erythema migrans (EM). Half of the patients who observed a tick bite subsequently reported EM. The duration from the onset of neurological symptoms to referral to hospital was remarkably long for patients with radiculoneuritis, whereas the onset of facial palsy led to a swift referral. Patients who were ≥ 50 years old had a significantly lower age-related risk of facial palsy without radicular symptoms.

CONCLUSION: In this study, winter as a low-risk season was not a reliable factor in ruling out LNB. This finding may be relevant when investigating the cause of facial palsy and radicular symptoms.

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TRIAL REGISTRATION: The study was approved by the Danish Data Protection Agency. The study was a data-register study, and therefore the approval of the National Committee on Health Research Ethics was not necessary.

Lyme neuroborreliosis (LNB) is an infection of the nervous system by the spirochete *Borrelia burgdorferi* sensu lato (BBSL) [1, 2]. In Denmark, 101 and 59 cases were reported yearly in 2011 and 2012, respectively, although the actual incidence is assumed to be much higher due to lack of reporting to central authorities [3] even if reporting is mandatory.

Borreliosis is a vector-borne infection. In Denmark, it is transferred by the tick *Ixodes ricinus*, and 5-20% of ticks are BBSL carriers [4]. Co-infection of ticks with different BBSL sub-species has been reported [5, 6]. The

tick usually needs to be fed for more than 24 hours for the bacteria to be transferred because they have to be activated by a blood meal to migrate from the intestinal system of the tick to its salivary glands.

The incidence of LNB generally shows great seasonal variation due to the lifecycle of the tick. The tick is active from early spring to late autumn. The incubation time of LNB usually varies from 3 to 6 weeks from the time of the tick bite to the appearance of the first symptoms. Typical symptoms of LNB are cranial nerve affection, facial palsy, painful radiculoneuritis and sub-acute meningitis. An infected individual commonly has initial radicular pain, which is often associated with the location of the tick bite and with nocturnal intensification. Later, different sensory and/or motoric deficits appear, such as paraesthesia and dysaesthesia, which may affect different parts of the body [7, 8]. Additionally, headaches are common, and nuchal rigidity has been reported [7, 9, 10]. The diagnosis of LNB is based on relevant clinical symptoms, cerebrospinal fluid (CSF) leucocytosis and intrathecal production of borrelia-specific antibodies [11], proven by a positive anti-*B. burgdorferi* immunoglobulin (Ig) M and/or IgG antibody index (AI) in CSF and serum samples. However, patients can remain seronegative for up to 6-8 weeks after the onset of symptoms [12]. Anti-*B. burgdorferi* IgG antibodies may persist in the spinal fluid for years after a primary and possibly sub-clinical infection [13]. The seroprevalence of *B. burgdorferi* antibodies can be relatively high in endemic regions [14].

With this study, we aimed to clarify the seasonal variation of LNB, including the history, symptoms, laboratory data and the clinical course of LNB in adults (≥ 16 years).

METHODS

All patients (≥ 16 years) examined and diagnosed with LNB at the Department of Neurology, Lillebaelt Hospital, in the period from 1 January 2003 to 25 September 2012 were included in the study. The identification of patients was based on information of a positive anti-*B. burgdorferi*-specific IgM and/or IgG antibody index obtained from the hospital's laboratory information system. Among these, the patients with CSF leucocytosis and no other causes of symptoms were included (n = 69).

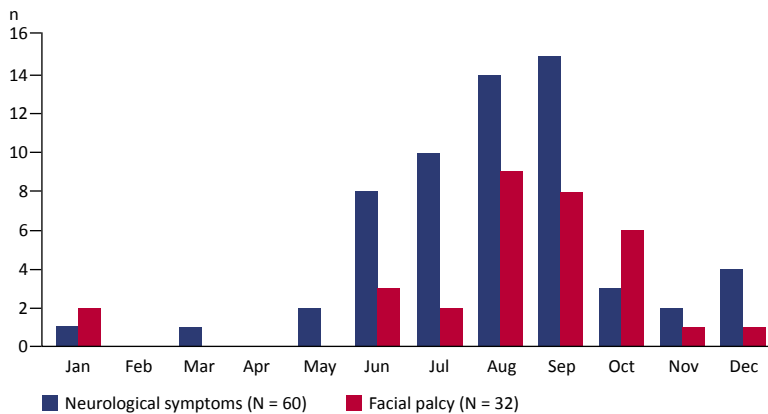
ORIGINAL ARTICLE

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FIGURE 1

Seasonal variation of onset of symptoms in the patients for whom data were available.



Patients admitted to other departments at the hospital were not included in the study. Due to the referral policy of the hospital in the study period, most patients with suspected LNB were admitted for diagnostic procedures at the Department of Neurology. The medical records of the included patients were examined thoroughly, and information was obtained on age, sex, tick exposition, EM, symptoms, duration of the symptoms and symptoms at discharge, including paraclinical data. The registered symptoms included radiculoneuritis, facial palsy or other cranial nerve involvement, headaches, nuchal rigidity, fever and mental changes. The paraclinical parameters included the lymphocyte count and protein content in CSF and the *B. burgdorferi*-specific IgM and IgG AI.

The lymphocyte count and protein content in CSF were obtained from a biochemical laboratory information system and were combined with an equivalent set of patient-specific data of anti-*B. burgdorferi*-specific antibodies in CSF and serum, which were obtained from the laboratory information system at the Department of Microbiology, Lillebaelt Hospital.

Data analysis and statistics

To detect potential age-related differences in symptoms, the patients were divided into two groups: those aged ≥ 50 years ($n = 38$) and those aged < 50 years ($n = 31$). The risk of radiculoneuritis, facial palsy and facial palsy without radicular symptoms were calculated, and the relative risk (RR) of these symptoms between the two groups was calculated with a 95% confidence interval (CI). The following formula was used when calculating the RR (95% CI): $RR = P_1/P_0$, $P =$ proportion, $\ln RR = \ln (P_1/P_0)$, standard error (SE) ($\ln RR$) = $\sqrt{1/a_1 - 1/n_1 + 1/a_0 - 1/n_0}$, 95% CI (RR) = $\exp(\ln RR \pm 1.96 \times SE (\ln RR))$.

When evaluating the significance of the results, the Z-score was calculated as follows: $\ln RR/SE (\ln RR)$, and a p-value of < 0.05 was considered significant.

Detection of *B. burgdorferi* immunoglobulin M- and immunoglobulin G-specific antibody production

The CSF was first screened with an IDEIA enzyme immunoassay (Oxoid, United Kingdom) for antibodies against *B. burgdorferi* flagellar antigens. If the initial test was positive, the serum and the CSF were tested simultaneously using the IDEIA enzyme immunoassay (Oxoid). The results of the immunoassay were expressed as optical densities (OD) and interpreted according to the manufacturer's instructions. To determine intrathecal synthesis of anti-*B. burgdorferi* antibodies, the AI was calculated using the formula $(OD_{CSF}/OD_{serum}) \times (OD_{CSF} - OD_{serum})$. An AI of ≥ 0.3 was considered positive and as an indication that the antibodies in the CSF were caused by intrathecal production and not spill-over from serum.

Trial registration: The study was approved by the Danish Data Protection Agency. The study was a data-register study and therefore the approval of the National Committee on Health Research Ethics was not necessary.

RESULTS

Among the 69 patients with a confirmed diagnosis, the male/female ratio was 42/27. The median age was 52 years (range: 17-80 years). Six patients (10%) had onset of neurological symptoms between December and March, and 3 patients (9%) had onset of facial palsy in December and January (**Figure 1**).

Among patients with a history of tick bite, 11 later noticed EM. Of those with no history of tick bite, 12 had EM. One patient developed multiple EM. Only half of the patients with available information had a history of tick bite or EM (**Table 1**).

Radiculoneuritis was the most common symptom (**Table 2**). Among 56 patients with radiculoneuritis, the associated symptoms varied, with 50 (89%) having pain, 42 (75%) having paraesthesia and 15 (27%) having various degrees of paresis of the extremities. Paresis did not occur without concomitant pain or paraesthesia. A total of 28 (50%) patients with radiculoneuritis had concomitant facial palsy and 14 (25%) had cranial nerve paresis (non-facialis). In the group of patients with available information ($n = 19$), the pain intensified at night in 16 (84%) of the patients.

One patient had monosymptomatic facial palsy. When multiple neurological symptoms were seen, facial palsy was never the initial symptom.

In addition to the physical symptoms, four patients had psychological symptoms, including depression and manic behaviour.



TABLE 1

	Patients for whom information was available, n	Patients with positive anamnesis, n (%)	Time from the event to the onset of neurological symptoms, weeks, median (range)	Time from the event to hospital referral, median (range)
Anamnesis of tick bite	46	23 (50)	6 (2-13)	8 (3-13)
Anamnesis of EM	45	23 (51)	1-2 (0-23)	5-6 (0-26)

Clinical data on the patients with tick bites and erythema migrans (EM).

A significantly lower risk of facial palsy without radicular symptoms was seen in the older age group (Table 3).

At the initial lumbar puncture, 14 (20%) patients had positive anti-*B. burgdorferi* IgM AI, 17 (25%) had positive IgG AI and 38 (55%) had both positive IgM and IgG AI.

The median leucocyte count was $219 \times 10^6/l$ (range: $5-1,152 \times 10^6/l$) at the time of the initial lumbar puncture, and the median protein level was 1.05 mg/l ($\pm 0.18 \times 4.67$ mg/l).

In the group of patients hospitalised for more than one day (n = 39), the median time of hospitalisation was nine (range: 2-21) days. The symptoms had improved at discharge in 74% (n = 29) of the patients and 8% (n = 3) had complete remission of symptoms.

DISCUSSION

In most cases, the onset of neurological symptoms in LNB was seen in July, August and September, as reported in earlier studies [7, 8, 15]. However, of note, the onset of symptoms occurred in almost every month of the year, apart from February and April. This is in line with other Danish studies [8, 10], and this finding emphasises that LNB should be a diagnostic consideration all year round if relevant symptoms are present. This is especially important with regard to facial palsy, where the season was reported to be a reliable factor for ruling out LNB [15, 16].

This study confirms the findings of earlier studies that the absence of an observed tick bite and/or EM is an unreliable negative predictor of LNB [7, 8, 10, 15]. A Swedish study showed that there was no significant difference between patients with LNB and Bell's palsy with regard to history of tick bites/EM [15].

As this was a retrospective study, there is a risk of recall bias. To minimise this risk, we excluded records where the subjects had expressed uncertainty about the time of the onset of symptoms, a tick bite, EM or symptoms. Interestingly, only 11 (48%) of the patients who reported a tick bite subsequently reported EM. If someone were aware of a tick bite, it would be natural to assume that the person would notice whether an expand-



TABLE 2

Distribution of symptoms in 69 patients.

	Patients with the symptom, n (%)	Time from the onset of symptoms to the initiation of treatment, median (range)
Radiculoneuritis	56 (81)	3 weeks (1 day-10.5 months)
Facial palsy	36 (52)	2 days (1-14)
Loss of sensation in all or parts of the innervation area of the trigeminal nerve	9 (13)	–
Diplopia	6 (9)	–
Headache	22 (32)	2 weeks (1 day-6 months)
Nausea	7 (10)	–
Vertigo	5 (7)	–
Fever	3 (4)	–
Uncharacterised hearing impairment	2 (3)	–
Anosmia	1 (1)	–
Hypogeusia	1 (1)	–
Unilateral paresis of the hypoglossus nerve	1 (1)	–
Nuchal rigidity	0	–



TABLE 3

Age-dependent association with the relative risk of different symptoms and prolonged symptoms.

	≥ 50 years, n (%) (N = 38)	< 50 years, n (%) (N = 31)	RR (95% CI)	p-value*
Radiculoneuritis	33 (87)	23 (74)	1.18 (0.94-1.50)	> 0.1
Facial palsy	18 (47)	18 (58)	0.81 (0.52-1.27)	> 0.2
Facial palsy without radicular symptoms	1 (3)	7 (23)	0.12 (0.02-0.90)	< 0.05

CI = confidence interval; RR = relative risk.

*) p < 0.05 is considered significant.

ing rash occurred at the site of the bite. The absence of observations of EM indicates that not all infections with *B. burgdorferi* result in an initial EM, which corresponds with earlier findings [17].

The symptoms of the patients in this study, as well as the relative incidence of the different symptoms, confirm the results of other studies on LNB [7-10]. However, in contrast to reports from other studies [7, 9, 10], none of the patients in the present study reported nuchal rigidity. Since the study only included patients from the



Picture of the spirochete *Borrelia burgdorferi*.

Department of Neurology, there is a risk of selection bias that could affect the presentation of symptoms among the patients, so that milder cases/cases without neurological symptoms may not have been included. In this context, it is notable that in the studied period, all adult patients with a positive anti-*B. burgdorferi*-specific antibodies index and indication of treatment were treated at the Department of Neurology.

A previous study described agitated behaviour in LNB patients, but this was attributed to pain and a lack of sleep [8]. In the present study, none of the patients with psychological symptoms had complaints of pain; they had low-grade sensibility disturbances, transitory diplopia, anosmia or hypogeusia.

The time from the onset of the symptoms to treatment was longer for radiculoneuritis than for facial palsy, which indicates that the more diffuse radicular symptoms in the former lead to a delay in diagnosis. Another Danish study found a corresponding delay in the diagnosis of radiculoneuritis, with a median delay of 27 days [10]. Thus, greater awareness of radicular symptoms as a sign of LNB may be warranted.

A significantly lower risk of facial palsy without radicular symptoms was found in the older age group, which indicates that this presentation of symptoms is more common in young people, but only eight patients presented with facial palsy without radicular symptoms, which is too few to draw any conclusions. In this study, all the patients were adults, over 16 years of age. Earlier studies reported differences in the symptoms of children and adults, respectively [8, 10]. A Danish study found that monosymptomatic facial palsy was a more common symptom in children than in adults [8] and this might also be the case with young versus older adults. A German study did not find a significant difference in the

number of patients > 50 and < 50 years with isolated facial palsy, but, unlike us, they reported a significantly higher number of radiculoneuritis symptoms among older patients [9]. The limited study material may explain why we found no significant difference.

In this study, the low-risk season did not seem to be a reliable factor for ruling out LNB. This finding may be relevant when investigating the cause of facial palsy and radicular symptoms.

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CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

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