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Systematic review

Lyme neuroborreliosis with encephalitis; a systematic literature review and a Scandinavian cohort study

Fredrikke Christie Knudtzen [1, 2, 3, *], Randi Eikeland [4, 5], Daniel Bremell [6, 7], Else Quist-Paulsen [8], Isik Somuncu Johansen [2, 3], Anne-Marit Solheim [9, 10], Sigurdur Skarphédinsson [1, 2, 3]

[1] Clinical Center for Emerging and Vector-borne Infections, Odense University Hospital, Odense, Denmark
[2] Department of Infectious Diseases, Odense University Hospital, Odense, Denmark
[3] Research Unit of Infectious Diseases, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark
[4] The Norwegian National Advisory Unit on Tick-Borne Diseases, Sørlandet Hospital, Arendal, Norway
[5] Faculty of Health & Sport Sciences, University of Agder, Norway
[6] Department of Infectious Diseases, Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Sweden
[7] Department of Infectious Diseases, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[8] Department of Microbiology, Oslo University Hospital Ullevål, Oslo, Norway
[9] Department of Neurology, Sørlandet Hospital, Kristiansand, Norway
[10] Department of Clinical Medicine, University of Bergen, Norway

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ABSTRACT

Background: Lyme neuroborreliosis (LNB) presenting with encephalitis is rare and scarcely described.
Objectives: To describe the available literature on LNB encephalitis and to characterize this patient group through a Scandinavian retrospective cohort study.
Data sources: Medline, Embase, Scopus, Cochrane library.
Study eligibility criteria: There was no discrimination on study type, time of publication or language.
Participants: **Review:** All articles with definite LNB and confirmed/possible encephalitis. **Cohort:** LNB cohorts from Denmark, Sweden and Norway 1990–2019 were screened for patients with encephalitis.
Methods: **Review:** Adhering to PRISMA guidelines; two authors extracted reviews and assessed quality of studies. **Cohort:** Data on demography, symptoms, cerebrospinal fluid findings, differential diagnostic examinations, treatment, residual symptoms, 1-year mortality were registered.
Results: **Review:** 2330 articles screened on title/abstract, 281 full texts, yielding 42 articles (case reports/series or cohort studies), including 45 patients from 18 countries spanning 35 years. Altered mental status ranged from personality changes and confusion to unconsciousness. Common focal symptoms were hemiparesis, ataxia and dysarthria; seven patients had seizures. Median time from symptom onset to hospital was 2 weeks (IQR 2–90 days). Of 38 patients with available follow-up after median 12 months (IQR 5–13), 32 had fully or partially recovered, two had died. **Cohort:** Thirty-five patients (median age 67 years, IQR 48–76) were included. The encephalitis prevalence was 3.3% (95% CI 2.2–4.4%) among 1019 screened LNB patients. Frequent encephalitis symptoms were confusion, personality changes, aphasia, ataxia. EEGs and neuroimaging showed encephalitis in 93.8% and 20.6%, respectively. Median delay from symptom onset to hospital was 14 days (IQR 7–34), with further 7 days (IQR 3–34) delay until targeted therapy. At follow-up (median 298 days post-treatment; IQR 113–389), 65.6% had residual symptoms. None had died.
Conclusions: This study shows that encephalitis is an uncommon, but likely overlooked clinical manifestation of LNB. As the high frequency of residual symptoms may be related to prolonged treatment delay, prompt LNB testing of patients with encephalitis in *Borrelia burgdorferi*-endemic areas should be considered. **Fredrikke Christie Knudtzen, Clin Microbiol Infect 2022;28:649**

* Corresponding author. Fredrikke Christie Knudtzen, Clinical Center for Emerging and Vector-borne Infections (CCEVI), Department of Infectious Diseases, Odense University Hospital, J.B.Winsloews vej 4, 5000 Odense C, Denmark.
E-mail address: fredrikke.christie.knudtzen@rsyd.dk (F.C. Knudtzen).

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Introduction

Lyme neuroborreliosis (LNB) is a neurological infection with the spirochete *Borrelia burgdorferi sensu lato*. *B. burgdorferi* can affect both the peripheral and the central nervous system (CNS), with the most common symptoms being painful radiculitis, peripheral facial nerve palsy and lymphocytic meningitis [1–3]. LNB is diagnosed based on neurological symptoms and cerebrospinal fluid (CSF) findings [1]. Even though most patients eventually recover, there is a risk of residual symptoms persisting after treatment. This risk is associated with the delay from symptom onset to treatment initiation [2,4,5].

Encephalitis, an inflammation of the brain parenchyma associated with neurological dysfunction, can be found in a wide range of infections, though usually associated with viral infections [6–8]. LNB presenting as encephalitis is scarcely reported in the literature, and often vaguely defined [1,3,9]. Unawareness of *B. burgdorferi* as a potential cause of encephalitis may have diagnostic and therapeutic consequences, and hence impair outcomes of this serious condition.

To increase the understanding of encephalitis in LNB, the objectives of this study were:

1. To describe the available data on LNB with encephalitis through a systematic literature review, focusing on symptoms and residual symptoms after treatment, and
2. To characterize patients with LNB presenting with encephalitis through a retrospective cohort study consisting of Danish, Swedish and Norwegian patients, describing demographic data (age, sex, comorbidities), clinical symptoms of encephalitis, paraclinical results (CSF, blood tests, electroencephalography (EEG), neuroimaging), time from symptom onset to treatment, residual symptoms at last follow-up and 1-year mortality

Material and methods

Sub-study 1—systematic literature review

Literature search

We conducted a systematic review of the literature adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (please see supplementary material: Appendix 1) [10]. Medline, Embase, Scopus and the Cochrane Library database were searched on 19 August 2020. We did not discriminate on study type, time of publication or language.

Study selection and data extraction

Two reviewers (S.S., F.C.K.) screened all titles and abstracts. All conflicts were resolved through discussions with a third reviewer (I.S.J.). Two reviewers screened all full texts (S.S., F.C.K. for English, Danish and Norwegian articles; F.C.K. with help from German, Russian, Polish, French, Serbian, Czech, Hungarian, Japanese, Brazilian and Italian native-speaking medical doctors for these languages). To be included in the review, enough details to fulfil both the criteria for definite LNB and for confirmed/possible encephalitis were required (Table 1) [1,8]. As the expectation was that mainly case reports would be included, and no predefined checklists were found eligible, checklists for descriptive data, outcome data and quality assessment were defined prior to study inclusion. Quality control of included studies was performed by two reviewers (S.S., F.C.K.), conflicts resolved through discussion with a third reviewer (I.S.J.). The protocol is published in PROSPERO (protocol nr.CRD42020191548).

Sub-study 2—retrospective cohort study

Study setting and population

Patients included in the study were retrieved from the three Scandinavian countries:

1. A Danish cohort through the Clinical Center for Emerging and Vector-borne Infections, Odense University Hospital, consisting of all patients registered with a positive *B. burgdorferi* intrathecal antibody index at the local Department of Clinical Microbiology. The cohort is ongoing, and patients from 1 January 1995 throughout 2020 were eligible for inclusion [2].
2. A Swedish cohort from the Department of Infectious Diseases, Sahlgrenska University Hospital, Gothenburg, consisting of patients with a positive CSF *B. burgdorferi* antibody test included in a previous study from 1988 to 2002, and patients included in a structured follow-up programme 2003–2012 [11,12].
3. Two Norwegian cohorts; one consisting of patients from three studies at the Hospital of Southern Norway and Stavanger University Hospital; The BOB study (children 2011–2014), the NevroBorreliosis treatment study (2004–2008) and patients evaluated for inclusion in a randomized, double-blinded treatment study (BorrSci) 2015–2020, the other a cohort from a study at Oslo University Hospital Ullevål of patients admitted with suspicion of acute CNS-infections between 2014–2016 [13–16].

Only patients fulfilling the criteria of both definite LNB and confirmed/possible encephalitis were included (Table 1). Medical charts for eligible patients were read and screened for fulfilment of the diagnostic criteria by a neurologist and/or infectious disease specialist before inclusion (R.E., D.B., E.Q.P., A.M.S., F.C.K.). Any conflicts were resolved through discussion with another author.

Data collection

By reviewing patient charts, clinical data was gathered on demographics (age, sex, co-morbidities; Charlson Comorbidity Index [17]), symptoms of encephalitis, other symptoms of LNB, responsiveness (Glasgow Coma Scale [18]), time from symptom onset to first hospital contact and treatment, course of disease including antibiotic treatment, treatment length, hospital admittance, admittance to an intensive care unit (ICU), follow-up duration, residual symptoms at last contact (including Modified Rankin Score where available [19]) and 1-year mortality. Of paraclinical data, CSF and peripheral blood test results, tests for microbiological differential diagnoses, neuroimaging (computed tomography (CT) and/or magnetic resonance imaging (MRI) of cerebrum) and EEG results were registered where available.

Borrelia burgdorferi testing

For detection of intrathecal synthesis of *B. burgdorferi* specific antibodies/CSF-*B. burgdorferi* antibodies, the second-generation IDEIA Lyme Neuroborrelioses test from Oxoid (Denmark and Kristiansand cohorts), the enzyme-linked immunosorbent assay for IgG/IgM antibodies to purified native *B. burgdorferi* flagellum from Dako (Sweden for CSF antibodies until 26.6.2006) and the LIAISON *Borrelia* IgG/*Borrelia* IgM Quant from DiaSorin (Oslo including calculating the intrathecal index using the Reiber formula, Sweden for CSF antibodies after 26.6.2006) were used. In serum, EIA (Sweden until 26.6.2006), the LIAISON (Oslo, Sweden after 26.6.2006, Denmark

Table 1
The definitions of definite Lyme neuroborreliosis and confirmed and possible encephalitis used throughout the study

Definite LNB	1. Neurological symptoms suggestive of LNB without other obvious reasons AND 2. CSF pleocytosis (>5 × 10^6/L) AND 3. intrathecal production of *Bb* antibodies[a]
Confirmed encephalitis	Major criterion (required): • altered mental status (decreased or altered level of consciousness, lethargy or personality changes) lasting ≥24 hr with no alternative cause identified AND ≥3 of the following minor criteria: • documented fever ≥38° within 72 hr before or after presentation • generalized or partial seizures not fully attributable to a pre-existing seizure disorder • new onset of focal neurological findings • CSF pleocytosis (>5 × 10^6/L) • abnormal brain parenchyma on neuroimaging suggestive of encephalitis • abnormality on electroencephalography that is consistent with encephalitis
Possible encephalitis	Fulfilling the major criterion and 2 minor criteria

Adapted from the European Federation of Neurological Societies and the International Encephalitis Consortium, respectively.
[a] In patients diagnosed prior to the introduction of the *Bb* intrathecal test, presence of *Bb* antibodies in CSF was considered sufficient.

2015–2020), the IDEIA (Denmark 1995–2010) and the Siemens Enzygnost Lyme link VlsE/IgG and Enzygnost Borreliosis/IgM assays (Denmark 2011–2014, Kristiansand) were used.

Statistics

Descriptive statistics were used to test significance between groups, using STATA version 16. Pearson's chi-squared test and Fisher's exact test for categorical variables, the Kruskal–Wallis test for non-normally distributed data for continuous variables with several means. A p value < 0.05 was considered statistically significant.

Ethics

The study is retrospective, with no patient contact. In Denmark the project was approved by the Danish Data Protection Agency (j.nr.2008-58-0035 and j.nr.19/18028), the Danish Health and Medicines Authority (j.nr.3-3013-631/1/) and The Regional Committees on Health Research Ethics for Southern Denmark (Project-ID S-20160143). In Sweden the study was approved by the Swedish Ethical Review Authority (D.nr.2020-06361). In Norway informed consent was obtained from all patients prior to study inclusion, and approvals were obtained by the Hospital of Southern Norway (ref.nr.20/10298=6-521) and Oslo University Hospital (ref.nr.20/20796).

Results

Sub-study 1

Study inclusion/exclusion

Of the 281 full texts read, studies were primarily excluded for not fulfilling the definitions of either LNB ($n = 54$), encephalitis ($n = 73$) or both ($n = 34$) (Fig. 1; references in supplementary material, Appendix 2). Due to lack of disclosure of patient symptoms and diagnostic findings, several studies referring to LNB with encephalitis were excluded, and only 42 studies with 45 patients fulfilled the inclusion criteria. Two eligible studies predated the *B. burgdorferi* spirochete discovery in 1982, and could therefore not fulfil the inclusion criteria for definite LNB, as the *B. burgdorferi* intrathecal antibody index did not exist at time of publication.

Description of included studies

The included studies were case reports ($n = 28$), case series ($n = 12$) or cohort studies ($n = 2$), with publication years spanning from 1985 to 2020. They originated from 18 different countries on three continents, with Germany most frequently represented ($n = 12$) (supplementary material: Appendix 2).

Patient characteristics and symptoms

The 45 included patients had a median age of 53 years (IQR 25–62 years), eight (17.8%) were children <18 years old, and 30 (66.7%) were male. The median CSF leucocyte count was 97 × 10^6/L (IQR 34–349 × 10^6/L). Information about the duration of symptoms at first hospital contact was available in 29 patients and was a median of 2 weeks (IQR 2 days – 3 months). This ranged from <1 day to, in one case, after debuting with a facial nerve palsy, symptoms of ataxia and personality changes progressed until the LNB diagnosis was confirmed by lumbar puncture 3 years after symptom debut. The level of details about encephalitis presentations varied greatly between studies (Table 2). Interestingly, ten (22.2%) patients experienced somnolence during their course of disease and eight (17.8%) were comatose. Moreover, 17 (37.8%) displayed personality changes ranging from euphoria to agitation/aggression and affect labilities. In 35 studies describing 38 patients, follow-up data was available. The majority had a full ($n = 15$, 39.5%) or partial ($n = 17$, 44.7%) recovery at last follow-up a median of 12 months (IQR 4.5–13 months) after hospital discharge. The most frequent residual symptoms were paresis ($n = 8$, 21.1%), cognitive deficits, e.g. memory impairment/learning difficulties ($n = 4$, 10.5%) and ataxia ($n = 3$, 7.9%). Two patients (5.3%) died (supplementary material: Appendices 2 and 3.)

Quality of studies

All studies fulfilled the criteria for definite LNB. In 32 of 42 studies, the patients fulfilled the criteria for confirmed encephalitis, while in ten studies only two minor criteria were fulfilled and they were classified as possible encephalitis. The number of investigations for differential diagnoses varied, but only two studies did not mention any differential diagnoses. Of alternative causes of encephalitis, *Treponema pallidum* ($n = 24$), herpes simplex virus (HSV) ($n = 19$), *Mycobacterium tuberculosis* ($n = 13$) and varicella zoster virus (VZV) ($n = 11$) were the most commonly investigated. Only six studies mentioned tick-borne encephalitis virus (TBEV) as a differential diagnosis. The patients received glucocorticoids and/or acyclovir prior to or concomitant with antibiotic therapy in 14 and 12 cases, respectively (supplementary material: Appendix 4).

Despite fulfilling the inclusion criteria, LNB as the cause of encephalitis could be questioned in ten studies; three studies described symptom progression after antibiotic treatment (two

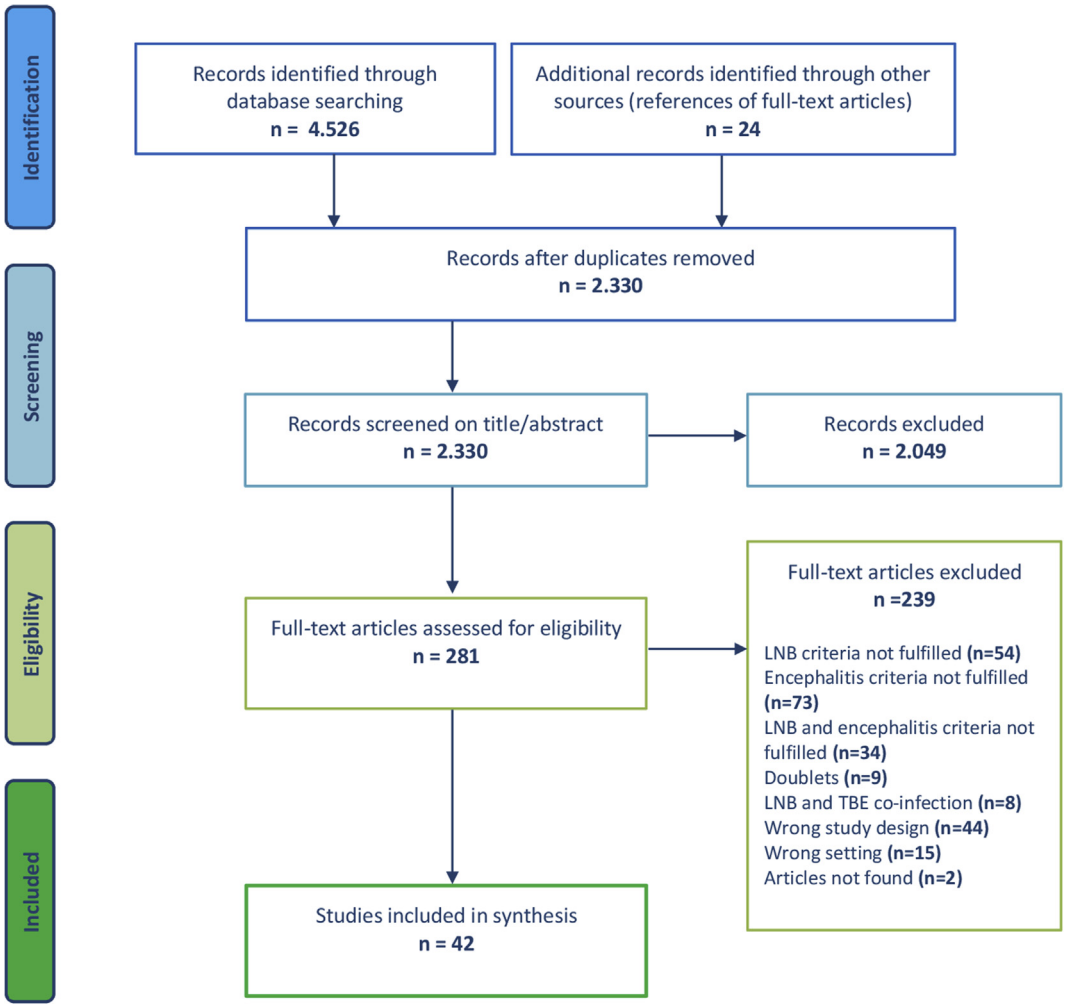

Fig. 1. Flowchart of study inclusion in a systematic review of Lyme neuroborreliosis presenting as encephalitis. Adapted from the PRISMA guidelines.

with fatal outcomes including one case suspicious of prion disease), two studies mentioned continued pleocytosis 8 and 12 months after relevant antibiotic treatment, respectively, one study found symptom remission after glucocorticoid therapy without antibiotic therapy given, another found spontaneous symptom remission before initiation of antibiotic therapy, and in three cases concomitant positive tests for HSV, VZV and cocaine suggested other possible causes of symptoms.

Sub-study 2

In all, 35 LNB patients fulfilled the inclusion criteria for encephalitis between 1990 and 2019. Of these, 16 were Danish, 15 Swedish and four Norwegian. Based on the 1019 LNB patients in the Danish, Swedish and Norwegian Kristiansand cohorts, the prevalence of encephalitis among the LNB patients was 3.3% (95% CI 2.2–4.4%). Using the number of patients in the Danish and Swedish cohorts and their patient uptake areas, the yearly LNB encephalitis incidence was estimated to be 0.93–1.35 cases/million inhabitants.

Patient characteristics

The median age of included patients was 67 years (IQR 48–76 years, range 9–86), 25 (71.4%) were male (Table 2). Two were children <18 years old. There were no significant differences in age, sex or comorbidities between patients from the different countries. Only one patient (2.9%) had symptom onset outside of the peak tick season (June to October).

Neurological symptoms

Altered mental status was most commonly seen as confusion/disorientation ($n = 25$) and/or personality changes ($n = 17$). Other common CNS symptoms were aphasia ($n = 9$), ataxia ($n = 7$) and hallucinations ($n = 7$). All but two patients had one or several of the typical LNB symptoms, e.g. radicular pain or peripheral facial nerve palsy.

Paraclinical findings

The median CSF leucocyte count was 177 $\times$ 10^6/L (IQR 54–409 $\times$ 10^6/L) (Table 3). Of neuroimaging, 34 patients had either a CT ($n = 14$) or MRI ($n = 20$) performed. Seven (20.6%) had changes compatible with encephalitis. These ranged from bilateral changes in the white matter ($n = 2$, temporo-parieto-occipital areas/around sella media and centrum semiovale) to frontal left sided oedema ($n = 1$), a right sided cortical lesion ($n = 1$), changes in right sided basal ganglia ($n = 1$) and vasculitis changes ($n = 2$, temporal lobes/widespread). In addition to these seven patients, two patients had changes compatible with normal pressure hydrocephalus. In all, 16 patients had an EEG performed during their course of disease, of whom 15 (93.8%) had abnormal findings consistent with

Table 2
Characteristics of two cohorts of patients with Lyme neuroborreliosis presenting with encephalitis: 45 patients found through a systematic literature review, and 35 patients from a cohort of Danish, Swedish and Norwegian patients seen between 1990 and 2019

Variable	Patients from systematic review ($n = 45$)	Patients from Scandinavian cohort ($n = 35$)
Age, years, median (IQR)	53 (25–62)	67 (48–76)
Children <18 years	8 (17.8)	2 (5.7)
Sex, male (%)	30 (66.7)	25 (71.4)
Charlson Comorbidity Index	$n = 22$	$n = 32$
0	15 (68.2)	17 (53.1)
1	5 (22.7)	12 (37.5)
≥2	2 (9.1)	3 (9.4)
Encephalitis symptoms		
Altered mental status		
Confusion/disorientation	20 (44.4)	25 (71.4)
Personality changes	17 (37.8)	17 (48.6)
Lethargy	4 (8.9)	9 (25.7)
Somnolence	10 (22.2)	3 (8.6)
Coma	8 (17.8)	0
Cognitive impairment[a]	12 (26.7)	24 (68.6)
Aphasia	3 (6.7)	9 (25.7)
Ataxia	11 (24.4)	7 (20.0)
Hallucinations	5 (11.1)	7 (20.0)
Dysarthria	9 (20.0)	4 (11.4)
Apraxia	1 (2.2)	3 (8.6)
Lowest registered GCS ($n = 16$)		
15	NA	5 (31.3)
13–14	NA	8 (50.0)
≤12	NA	3 (18.8)
Seizures	7 (15.6)	4 (11.4)
Other LNB symptoms		
Radicular pain	10 (22.2)	27 (77.1)
Headache	16 (35.6)	22 (62.9)
Fatigue	11 (24.4)	22 (62.9)
Dizziness	5 (11.1)	19 (54.3)
Paresis	23 (51.1)	11 (31.4)
Cranial nerve palsy	11 (24.4)	10 (28.6)
Meningitis	13 (28.9)	7 (20.0)
Fever	16 (35.6)	8 (22.9)

Data are presented as *n* (%) unless stated otherwise. GCS, Glasgow coma scale; IQR, interquartile range; LNB, Lyme neuroborreliosis; NA, not applicable.
[a] Memory loss, concentration difficulties.

Table 3
Paraclinical results in 35 patients with Lyme neuroborreliosis presenting with encephalitis from Denmark, Sweden and Norway between 1990 and 2019

Variable	Reference intervals	Number of patients with registered results	Number of patients positive/above normal range, *n* (%)	Median (IQR)
Cerebrospinal fluid				
Leucocytes, $\times 10^6$/L	0–5	35	35 (100.0)	177 (54–409)
Protein, g/L	0.2–0.6	31	23 (74.2)	1.2 (0.6–2.4)
Glucose, mmol/L	—	26	—	3.1 (2.4–4.3))
Borrelia burgdorferi IgM	Negative	34	24 (70.6)	
B. burgdorferi IgG	Negative	35	33 (94.3)	
Oligoclonal bands	Negative	19	18 (94.7)	
Cytology	Negative	18	0	
Microscopy for bacteria	Negative	18	0	
PCR herpes simplex virus	Negative	27	0	
PCR varicella zoster virus	Negative	25	0	
PCR enteroviruses	Negative	20	0	
Treponema pallidum Ab	Negative	13	0	
PCR Epstein Barr virus	Negative	11	2 (18.2)	
PCR cytomegalovirus	Negative	8	0	
Peripheral blood				
B. burgdorferi IgM Ab	Negative	33	19 (57.6)	
B. burgdorferi IgG Ab	Negative	34	30 (88.2)	
Leukocytes, $\times 10^9$/L	3.5–8.8	35	12 (34.3)	7.6 (6.4–10.5)
C-reactive protein, mg/L	<10	31	12 (38.7)	
Tick-borne encephalitis virus Ab	Negative	16	0	
Anaplasma phagocytophilum Ab	Negative	11	0	
Rickettsia spp. Ab	Negative	11	0	
TB interferon-gamma	Negative	8	0	
HIV Ab/Ag	Negative	6	1 (16.7)[a]	
T. pallidum Ab	Negative	4	0	

Ab, antibodies; Ag, antigen; IQR, interquartile range; PCR, polymerase chain reaction; TB, mycobacterium tuberculosis complex.
[a] Known HIV positive.

encephalitis. EEG was performed in significantly more patients in the time-period 2006e2019 compared with 1990e2005 (13 vs. 3 patients, p 0.01).

Microbiological investigations

Of the 20 Danish and Norwegian patients with a registered *B. burgdorferi* intrathecal index, nine had IgG antibodies only, two had IgM antibodies and nine had both IgM and IgG antibodies present. Of the remaining 15 Swedish patients with CSF *B. burgdorferi* antibodies, two had only IgG antibodies present and 13 had both IgM and IgG antibodies. In serum, three patients (8.6%) did not have either IgM or IgG antibodies present. Of these, one had a positive *B. burgdorferi* IgG intrathecal index which remained positive at a new lumbar puncture 26 days later, still without serum antibody response. The second patient had an initially positive *B. burgdorferi* IgM intrathecal index, but a re-puncture 15 days later revealed a positive intrathecal index for both IgM and IgG as well as an IgG response in serum. The last patient had no anti-*Borrelia* antibodies in serum at admittance, while both IgM and IgG in CSF were positive. Serum taken 19 days later revealed seroconversion with high IgG titre. Extensive evaluation of other causes of encephalitis was performed in all patients in the cohort (Table 3). Another cause of encephalitis was not found in any of the patients, as the two positive Epstein–Barr virus PCR-tests were considered to be reactivation without clinical significance.

Course of disease

The median delay from neurological symptom onset to first hospital contact was 14 days (IQR 7–34 days). All patients but two were admitted to hospital, of whom nine were admitted more than once. Only three patients required observation in an ICU. After the first hospital contact, the median delay before initiation of antibiotic therapy was 7 days (IQR 3–34 days). This was a median of 1 day after lumbar puncture (IQR 0–3, range 0–49). There was no significant difference in treatment delay between the three countries. After confirmation of LNB, treatment consisted of oral doxycycline ($n = 15$), intravenous ceftriaxone ($n = 4$), intravenous penicillin G ($n = 3$) or a combination thereof ($n = 13$). The median treatment duration was 14 days (IQR 10–21 days), significantly shorter in Swedish patients (median 10 days, IQR 10–14 days) compared with in Danish and Norwegian patients (median 21 days, IQR 14–21 days, p 0.006). In ten patients, the medical charts revealed doubts about the diagnosis after the initial results. Of these, six patients (60%) underwent a second lumbar puncture to confirm the LNB diagnosis, and six patients (60%) were tested for other pathogens after LNB was diagnosed. There was no significant association between displaying typical LNB symptoms of radicular neuritis and/or peripheral facial nerve palsy and questioning of diagnosis (p 0.14).

Follow-up and outcomes

The majority of patients responded to the treatment within one week ($n = 17$) or one month ($n = 16$) after treatment initiation. Three patients had no follow-up registered. Of the remaining 32 patients, their last follow-up was a median 298 days after antibiotic treatment initiation (IQR 113–389 days). Here, 21 patients (65.6%) had residual symptoms; cognitive impairment (concentration difficulties, impaired memory) ($n = 7$), fatigue ($n = 5$), ataxia ($n = 4$), paresis ($n = 3$) and neuropathic pain ($n = 2$). Of the 31 patients in whom the Modified Rankin Score could be calculated, 11 (35.5%) had a score of $\geq$2, indicating neurological disabilities affecting activities of daily life. None of the patients had died one year after treatment initiation.

Discussion

We have, with this combined systematic literature review and cohort study, provided a detailed description of the presentation and course of LNB encephalitis. Our most important findings are the many clinical presentations of encephalitis due to *B. burgdorferi*, the delay from hospital presentation to appropriate treatment, and the high risk of residual symptoms after infection.

Both in the systematic review and in the cohort, a wide range of clinical presentations of encephalitis was found, from slowly progressing neuropsychiatric symptoms to acute loss of consciousness. There were more patients from the systematic review with severely impaired consciousness (somnolence and coma) compared with the cohort, and the latter group displayed radicular pain and symptoms of cognitive impairment more commonly. When interpreting these results, the study approach must be considered; while the patients from the literature review had clinical presentations deemed interesting enough to be published in case reports/case series, the cohort patients' symptoms were found through chart reviews where all data was entered into a detailed database. The wide range of symptoms found, together with unawareness of LNB as cause of encephalitis and the many non-infectious and infectious differential diagnoses, may explain the relatively long duration found from symptom onset to targeted treatment.

The few cases found in the extensive systematic literature review combined with the low prevalence rate of 3.3% in the Scandinavian LNB cohort confirm that encephalitis is indeed a rare presentation of LNB. Even so, an important finding was the globally widespread distribution of LNB encephalitis, illustrating that LNB should be considered as a differential diagnosis in patients with encephalitis in all *Borrelia*-endemic parts of the world. Today, a *B. burgdorferi* intrathecal antibody index test is generally not recommended as a routine test in encephalitis guidelines in adults, but as part of second line investigations [8,20]. This despite the therapeutic consequences of a timely treatment and the large proportion of encephalitis cases of unknown aetiology, even in *Borrelia*-endemic areas [20,21]. A Swiss study including encephalitis patients >15 years old and the Oslo cohort both found a 10% LNB prevalence among encephalitis-patients [15,22]. This is in line with our findings of 0.93–1.35 LNB encephalitis cases per million inhabitants and the Danish prevalence of 1.4 infectious encephalitis cases per year among adults [23].

In the Scandinavian cohort, all patients but one with available EEGs had abnormalities consistent with encephalitis. Abnormal EEGs were more frequent than described in other causes of infectious encephalitis [24,25]. Though no specific EEG patterns of LNB could be established, this finding encourages more use of EEG in LNB patients with symptoms compatible with encephalitis. We found a broad range of neuroimaging changes, both in the patients from the literature review and in our cohort: from localized enhancement to widespread bilateral changes and vasculitis patterns. Unlike in HSV-1-encephalitis, where edema and hemorrhage in the temporal lobes are pathognomonic, no dominating neuroradiological pattern was observed [26]. This is in accordance with a previous report on neuroimaging patterns in LNB, and suggests that *Bb* spirochetes do not have a predilection for a specific part of the brain parenchyma [27].

Only 16 patients in the cohort and six in the review were tested for TBEV. TBEV is present with increasing incidence in all Scandinavian countries and in the majority of the countries represented in the systematic review [28–30]. Considering tick-bites were the cause of all the patients' encephalitis symptoms, one would expect more patients to have been tested concomitantly for *B. burgdorferi* and TBEV. However, due to the retrospective study design and the

fact that several of the included studies date back 20–30 years, no conclusions can be drawn from this finding.

The diagnosis of LNB as cause of encephalitis was questioned by clinicians in nearly one third of cases in our cohort. All patients responded to treatment, and no other causes of encephalitis was found in any of the patients, as shown in Table 3. In the literature review, a considerable part of the patients received acyclovir and/or glucocorticoids concomitant with antibiotics. This might have been pending test results or following guidelines for empiric meningoencephalitis treatment, but as many treatment courses were continued throughout the antibiotic course, it was likely due to doubt about the diagnosis [31]. As the *B. burgdorferi* intrathecal antibody index assays has shown a high specificity of 97–99%, and all patients had pleocytosis, the risk of false positive tests among the patients must be considered low [32]. A lack of publications about LNB encephalitis in the medical literature is likely to have contributed to doubting the diagnosis. Questioning a rare diagnosis is very important and necessary, however, it should not lead to a delayed treatment.

The only registered deaths from encephalitis were found in the literature review; one case from The Netherlands with locked-in syndrome despite relevant antibiotic treatment, where the autopsy revealed demyelinating lesions throughout the CNS, and one Polish case that fulfilled our inclusion criteria, but where the clinical and pathological findings were suspicious of prion disease. None of the cases in our cohort died within one year of LNB diagnoses. This suggests a low mortality in LNB encephalitis cases where patients have received targeted therapy, compared with other causes of infectious encephalitis [20,33]. Despite the low mortality, more than half the patients in the cohort had residual symptoms: one-third with neurological disabilities affecting daily life - at last hospital contact almost a year after encephalitis. This risk of sequelae is higher than in most LNB cohorts, and comparable to the risk of sequelae after viral encephalitis in similar settings [20,33,34].

The strengths of our systematic literature review are the strict adherence to the PROSPERO protocol, and the thoroughness of the review. We did not discriminate on language, which would have excluded 93 of the 281 full texts eligible for inclusion. The protocol including the full search strategy is published in PROSPERO and therefore fully reproducible. One strength of the cohort is the inclusion of patients from all three Scandinavian countries, thus ensuring generalizability of the results in the absence of national registers of LNB or encephalitis. Strict definitions for both LNB and encephalitis were used, thus limiting the risk of patient selection bias. We believe that through linking this thorough literature review with the description of the cohort, we present the most solid evidence of an association between LNB and encephalitis to date.

Of limitations to the study, the literature review included study designs with low grade of evidence. This was expected due to the rarity of the disease, but meant that no meta-analysis could be performed. Our study inclusion criteria are based on guidelines for LNB and encephalitis published in 2010 and 2013, respectively [1,8]. The majority of the studies in the literature review were published prior to these guidelines, in a time without consensus criteria for encephalitis. Not fulfilling the subsequently published criteria led to exclusion of several relevant studies with possible LNB encephalitis. European LNB guidelines requiring evidence of *B. burgdorferi* in the CSF was used, which led to exclusion of several American studies where they traditionally rely on serum *Borrelia* antibodies. The Swedish cohort patients were included based on patient symptoms, pleocytosis, treatment response and CSF *B. burgdorferi* antibodies, as the intrathecal antibody index test was not used at time of study inclusion. In the literature review, all studies reporting concomitant cases of TBEV and LNB were excluded, due to the same mode of microbial transmission and the possibility of encephalitis being caused by TBEV. Our cohort study is retrospective going back 30 years in time, with limited available data on some of the patients. As we only had access to hospital charts, we do not know the number of contacts with the primary healthcare sector before hospital admittance.

In conclusion, our findings show that encephalitis is an uncommon, but likely overlooked clinical manifestation of LNB. The high frequency of residual symptoms may be related to the prolonged diagnostic and treatment delay. Due to the potentially serious outcome of this CNS infection, these findings call for prompt LNB testing of all patients with encephalitis in *B. burgdorferi* endemic areas.

Transparency declaration

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Access to data

The literature search strategy is available from PROSPERO (protocol nr. CRD42020191548). The dataset generated for the cohort study is not publicly available due to the Danish Data Protection Law in accordance with the study approval by the Danish Data Protection Agency (j.nr. 19/18028). It is available from the corresponding author upon reasonable request.

Author contributions

Conception and design: S.S., I.S.J., F.C.K. Acquisition of data: F.C.K., R.E., D.B., E.Q.P., A.M.S. Interpretation of data: F.C.K., R.E., I.S.J., S.S. Drafting the article: F.C.K., R.E., D.B., I.S.J., E.Q.P., A.M.S., S.S. All authors read and approved of the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.11.001.

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