Journal of Infection 85 (2022) 507–512

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Original Article

No correlation between symptom duration and intrathecal production of IgM and/or IgG antibodies in Lyme neuroborreliosis – a retrospective cohort study in Denmark

Ingrid Krogen[a,b,*], Sigurdur Skarphédinsson[a,b,c], Thøger Gorm Jensen[a,b,d], Fredrikke Christie Knudtzen[a,b,c]

[a] Clinical Center for Emerging and Vector-borne Infections, Odense University Hospital, Odense, Denmark
[b] Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark
[c] Department of Infectious Diseases, Odense University Hospital, Odense, Denmark
[d] Department of Clinical Microbiology, Odense University Hospital, Odense, Denmark

ARTICLE INFO

Article history:
Accepted 15 August 2022
Available online 16 September 2022

Keywords:
Lyme neuroborreliosis
Borrelia burgdorferi sensu lato
Cerebrospinal fluid
Intrathecal borrelia burgdorferi antibody index

SUMMARY

Objectives: In Europe, a definite diagnosis of Lyme neuroborreliosis (LNB) requires intrathecally produced *Borrelia*-specific antibodies. We aimed to examine if the time from symptom debut to lumbar puncture (LP) correlated with findings of intrathecal production of *Borrelia*-specific IgM and/or IgG antibodies in LNB

Methods: A retrospective study of 544 patients with a positive *Borrelia burgdorferi* antibody index (Bb-AI) analysed at the Department of Clinical Microbiology, Odense University Hospital, Denmark, between 01.01.1995 and 31.12.2020

Results: The delay from symptom onset to LP for patients with positive Bb-AI IgM was 30 days (IQR 14–95 days), IgG 24 days (IQR 11–62), IgM+IgG 24 days (IQR 14–48), $P = 0.098$. Ninety-three patients had a second LP after median 125 days (IQR 28–432) and 25 had a third LP after median 282 days (IQR 64–539). Most patients (66.7%) did not convert from their initial intrathecal antibody finding. The prevalence of different clinical manifestations differed significantly between the three Bb-AI groups.

Conclusions: Intrathecal *Borrelia*-specific antibody production did not follow the typical immune response of initial IgM production followed by IgG production. Diagnosis of LNB stage should not be based on the type of antibodies found in the cerebrospinal fluid.

Introduction

Lyme borreliosis is a vector-borne disease caused by spirochaetes of the *Borrelia burgdorferi* (*Bb*) sensu lato complex [1]. Lyme borreliosis has various distinct symptom manifestations, and 10–15% of European patients develop Lyme neuroborreliosis (LNB) [2].

The *Bb* antibody index (Bb-AI) is considered the gold standard for diagnosing LNB as it has a reported sensitivity of >90% six weeks after the onset of neurological symptoms [3]. Despite completed antibiotic treatment, *Bb* antibodies can persist in the cerebrospinal fluid (CSF) for months to years [1, 3-6]. Therefore, a positive Bb-AI can only be interpreted as an active or a resolved infection based on additional CSF findings and the clinical picture.

The human adaptive immune system typically produces IgM antibodies 1–2 weeks after a pathogen enters the body [7]. Hence, the finding of IgM antibodies in conventional blood serology is usually an indication of an early, active infection. The immune system later begins to produce IgG antibodies, indicating a continued, chronic or resolved infection [7]. This interpretation is frequently extended to the *Bb* antibody index in CSF. The picture is more complex among LNB patients, however. The presence of *Bb* IgM and IgG antibodies in serum is of limited clinical value in diagnosing LNB in *Borrelia*-endemic areas due to the persistence of antibodies for months to years after treatment and the lack of specificity of *Borrelia* IgM [1]. With few data available, it is unclear if the time from symptom onset to diagnostic lumbar puncture (LP) correlates with the type of *Bb* antibodies found in the CSF as one would expect in

* Corresponding author at: J. B. Winsloews vej 4, 5000 Odense C, Denmark.
E-mail address: ingrid.l.krogen@live.no (I. Krogen).

https://doi.org/10.1016/j.jinf.2022.08.045

blood. Furthermore, there is limited knowledge about the clinical presentation of symptoms and sequelae in relation to intrathecal *Borrelia*-antibody profiles.

This study aimed to examine if time from symptom debut to diagnostic lumbar puncture corresponded with findings of intrathecally produced *Bb* IgM and IgG antibodies in patients with LNB. We hypothesised that, unlike in most other infections, there is no correlation between LNB disease duration and intrathecal *Bb* IgM and IgG antibody production.

Methods

Study design and participants

This retrospective cohort study included all patients from the Danish islands of Funen, Langeland and Ærø who fulfilled the criteria for possible or definite LNB including a positive Bb-AI IgM or IgG analysed at the Department of Clinical Microbiology at Odense University Hospital (OUH) between 1.1.1995 and 31.12.2020. Patient data were collected from paper and electronic records and were entered into an electronic database. More information on the study population is available in a prior publication [8]. All LPs, including repeat LPs, were performed on the clinician's request.

Definitions

The diagnostic criteria for definite LNB were a) the presence of typical neurological symptoms, b) CSF pleocytosis $\geq 5 \times 10^6$ cells/L and c) a positive Bb-AI [3]. Patients that fulfilled only two criteria were defined as having possible LNB. The pre-hospital delay was defined as the time from onset of neurological symptom to first hospital contact. The hospital delay was defined as the time from first hospital contact to diagnostic LP, and the diagnostic delay was defined as the time from symptom onset to diagnostic LP. A sequela was defined as an objective finding of a residual neurological symptom and/or subjective complaint of fatigue, concentration difficulties and/or memory impairment.

Borrelia burgdorferi analysis

All *Bb* antibody analyses were performed according to Danish guidelines on Lyme borreliosis diagnosis [9].

Borrelia burgdorferi antibody index

Bb-AI was measured with a second-generation flagella antigen-based capture enzyme immunoassay (IDEIA Lyme Neuroborreliosis, Oxoid, Hampshire, UK) [10]. This Bb-AI method is a capture EIA in which the ratio of anti-*Bb*-specific versus total antibody (of the same class) is determined separately for both CSF and serum, and it thus measures the ratio between the proportions of antibodies specific for *Borrelia* in each compartment rather than the ratio between the concentrations of *Borrelia* antibodies. An elevated AI indicates specific *Borrelia* intrathecal antibody production. Intrathecal production of *Bb* antibodies was assessed by simultaneously analysing CSF and serum samples extracted within 24 h of each other and then calculating the index according to the formula Bb-AI = $(OD_{CSF}/OD_{serum})^*(OD_{CSF}\text{-}OD_{serum})$ for IgG and IgM, respectively, where OD is optical density. Only index values ≥ 0.3 in combination with $OD_{CSF} \geq 0.15$ were regarded as positive [10].

Borrelia burgdorferi serum antibodies

Independently of the Bb-AI, *Bb* antibodies in serum (S-*Borrelia*) were analysed using the IDEIA *Bb* IgG and IgM (Oxoid, Hampshire, UK) 1995–2010, Siemens Enzygnost Lyme link VlsE/IgG and Enzygnost Borreliosis/IgM (Siemens, Marburg, Germany) 2011–2014, and LIAISON *Borrelia* IgG/*Borrelia* IgM Quant (DiaSorin, Italy) 2015–2020.

Table 1
Baseline characteristics of 544 patients with Lyme neuroborreliosis. Data are presented as number (% of total) unless otherwise indicated.

Characteristics	No. (%)
Age, years*	50 (15 – 64)
Children <18 years	145 (26.7)
Sex	
Male	321 (59.0)
History of tick bite	201 (37.0)
Erythema migrans	111 (20.4)
Symptoms	
Radicular pain	359 (66.0)
Cranial nerve palsy	237 (43.6)
Paresis	59 (10.9)
Sensibility disturbances	33 (6.1)
Cognitive symptoms	25 (4.6)
Headache	162 (29.8)
Dizziness	41 (7.5)
Fever	119 (21.9)
Headache, neck stiffness & fever	27 (5.0)
Fatigue	91 (16.7)
Weight loss	38 (7.0)
Pre-hospital delay, days*	20 (8 – 45)
Hospital delay, days*	1 (0 – 8)
Sequelae	156 (28.7)
1-year mortality	2 (0.4)

* Median (interquartile range).

Statistical methods

Results were analysed using Stata version 16.1. Data were described using median and interquartile ranges (IQR). The Pearson's χ^2 test (binary data) and *t*-test (continuous data) were used to test for differences between groups in normally distributed data. The Kruskal-Wallis equality of population rank test and Mann–Whitney–Wilcoxon test were used to test for differences between groups in non-normally distributed data. Logistic regression adjusted for time from neurological symptom onset to diagnostic LP was used to test for differences between two groups with binary outcomes. A *P* value <0.05 was considered statistically significant.

Ethics approval

The study was retrospective with no patient contact. It was approved by the Danish Data Protection Agency (j.nr.2008–58–0035 and 19/18,028), 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-20,160,143).

Results

Patient characteristics

A total of 544 patients were included. Three patients were included twice as they were diagnosed with LNB and fulfilled the inclusion criteria on two distinct occasions years apart. The median age was 50 years (IQR 15–64 years), 145 patients (26.7%) were <18 years and 59.0% were male (Table 1). 83.3% had no comorbidities, 37.0% had a history of a tick bite and 20.4% recalled having an erythema migrans (EM). Based on presence and absence of intrathecal *Bb* IgM and IgG antibodies, the patients were divided into three

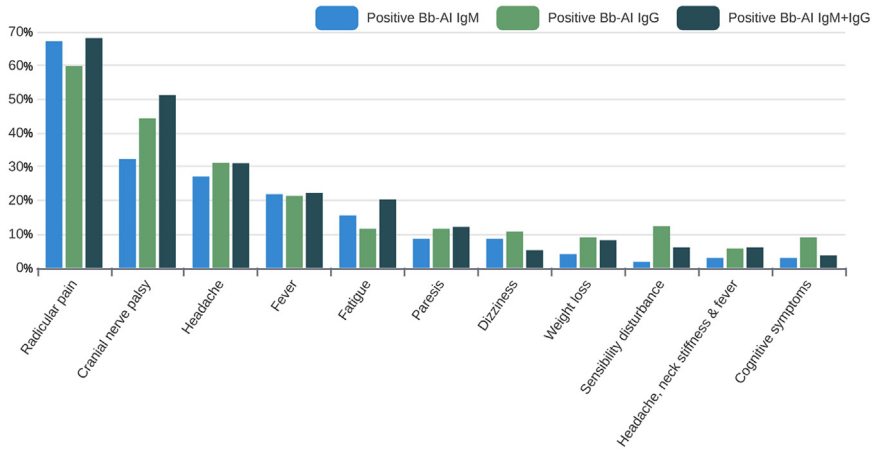

Fig. 1. Display of different symptoms in 544 patients with Lyme neuroborreliosis based on findings of positive *Borrelia burgdorferi* intrathecal antibody index (Bb-AI) IgM, IgG or IgM+IgG. Each bar represents the number of patients in each Bb-AI group (in %) with a particular symptom.

Table 2
Diagnostic delay (in days) for 544 patients with Lyme neuroborreliosis related to *Borrelia burgdorferi* intrathecal antibody index (Bb-AI). Data are presented as medians and interquartile ranges.

	Positive Bb-AI IgM		Positive Bb-AI IgG		Positive Bb-AI IgM+IgG		P
	No. of patients	Diagnostic delay	No. of patients	Diagnostic delay	No. of patients	Diagnostic delay	value
Adults (*n* = 399)	141	33 (15–97)	94	31 (15–93)	164	29 (18–58)	0.284
Children (*n* = 145)	33	15 (5–35)	28	7 (4–18)	84	16 (8–31)	0.090
All patients (*n* = 544)	174	30 (14–95)	122	24 (11–62)	248	24 (14–48)	0.098

groups: IgM-group (n = 174), IgG-group (n = 122) and IgM+IgG-group (n = 248).

Symptoms

The most frequent symptoms were radicular pain (66.0%), cranial nerve palsy (43.6%) and headache (29.8%) (Fig. 1). Symptom presentation differed significantly between the three groups: the patients in the IgM+IgG-group had cranial nerve palsy more frequently (51.2%) than patients in the IgM-group (32.2%) and IgG-group (44.3%), P<0.001. Patients in the IgG-group had a higher prevalence of cognitive symptoms (9.0%) compared to the IgM-group (2.9%, P = 0.012) and of sensibility disturbances (12.3%) compared with the IgM-group (1.7%, P<0.001) and IgM+IgG-group (6.1%, P = 0.041). There were no statistically significant differences between the groups in prevalence of radicular pain, headache or fever (see Supplementary Material 1).

Course of disease

The median diagnostic delay was 25 days (IQR 14–61 days). In children <18 years, the diagnostic delay was 14 days (IQR 5–30 days), which was significantly shorter compared to adults (30 days, IQR 16–80 days), P = 0.003. No significant difference in diagnostic delay was found between the IgM-group (median 30 days, IQR 14–95 days), IgG-group (median 24 days, IQR 11–62 days) and IgG+IgM-group (median 24 days, IQR 14–48 days) (P = 0.098) (Table 2).

In 156 (28.7%) patients, residual symptoms were present at the time of last hospital contact. There was no statistically significant difference in prevalence of sequelae between the IgM-group (27.0%), the IgG-group (31.2%) and the IgM+IgG-group (28.6%), P = 0.741.

Multiple lumbar punctures

In 93 (17.1%) of the 544 LNB patients, a second LP was performed a median 125 days (IQR 28–432 days) after the first LP (Fig. 2). Twenty-five patients had a third LP performed a median 282 days (IQR 64–539 days) after the second LP. Five patients had a fourth LP performed a median 91 days (IQR 72–238 days) after the third LP. Two patients had a fifth LP performed. Of note, six patients had a positive Bb-AI IgM at three subsequent LPs without converting to Bb-AI IgG positivity, including two patients with 1996 and 3341 days between first and last LP.

Of the 19 (20.4%) with negative Bb-AI in the second and third LP, the quantitative serum *Bb* antibody measurement was available in five patients. Four patients had a reduced OD_{CSF} and in three patients, this was accompanied by a decreased OD_{serum} compared to the prior LP. One patient had an increased IgM OD in both CSF and serum, resulting in a lower ratio and therefore a negative Bb-AI IgM. In the diagnostic LP, a CSF leukocyte count was available in 18 patients; all had pleocytosis. 14/18 (78%) had a normalised leukocyte count in the repeat LP, and the remaining four patients had a considerable decrease in cell count.

CSF pleocytosis

Fifty-seven (10.6%) of the 540 patients with a cell count available in their chart had no pleocytosis. In the IgM-group, fewer patients had pleocytosis (n = 136/174, 78.2%) compared to the IgG-group (n = 107/119, 89.9%, P = 0.009) and the IgM+IgG-group (n = 240/247, 97.2%, P<0.001). Of the 57 patients without pleocytosis, 22 had the LP performed more than six months after symptom onset and 13 had the LP within five days after symptom onset, five patients had pleocytosis in a LP performed prior to the diagnostic LP (not analysed for Bb-AI) and three had received antibiotic treatment prior to LP (see Supplementary Material 2). Excluding the 57 patients without pleocytosis did not change the non-significant difference in diagnostic delay between the IgM-group, the IgG-group and the IgM+IgG-group (P = 0.270).

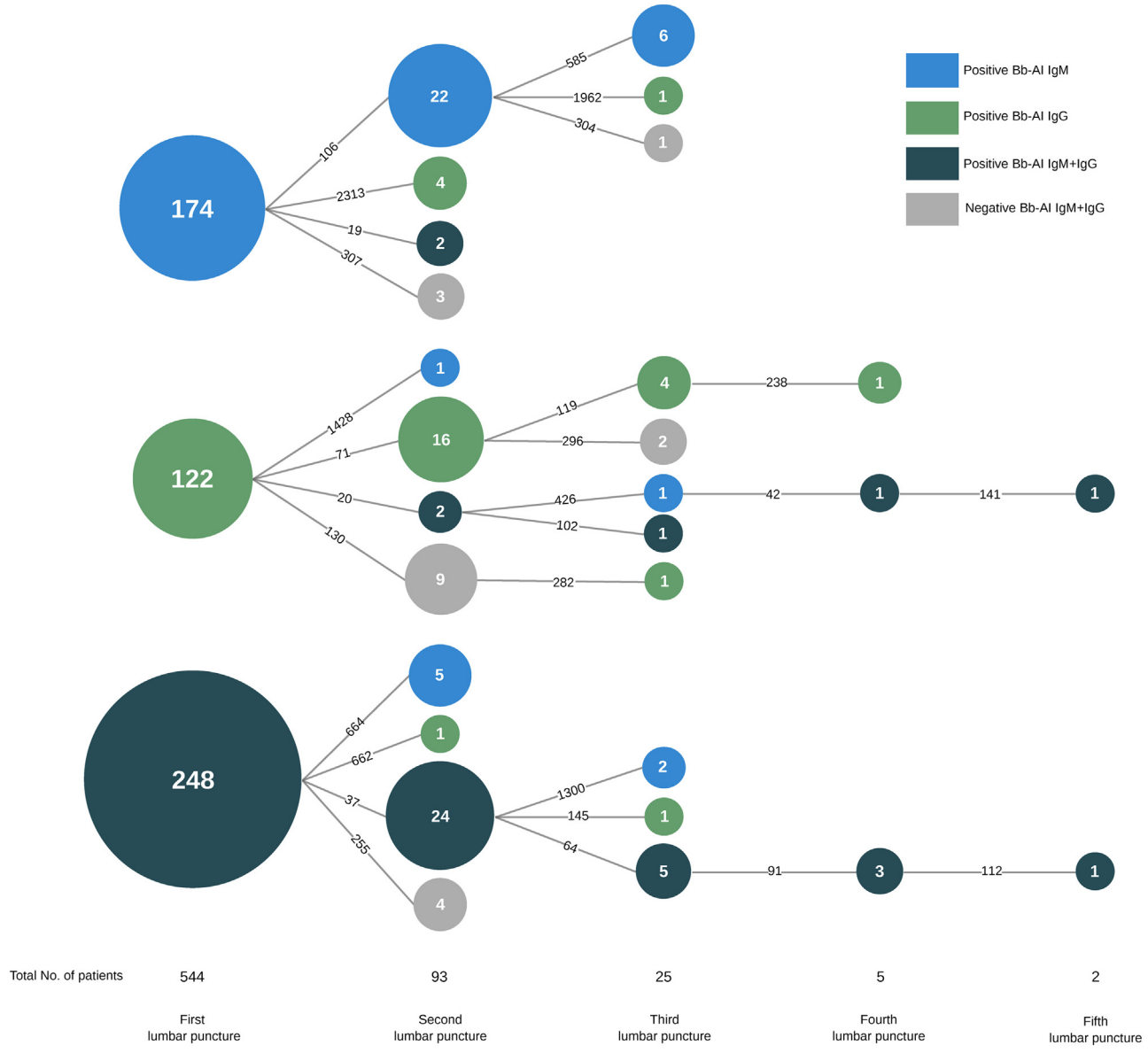

Fig. 2. Number of patients with positive *Borrelia burgdorferi* intrathecal antibody index (Bb-AI) IgM, IgG, IgM+IgG, and negative IgM+IgG at the time of first to fifth lumbar puncture among 544 patients with Lyme neuroborreliosis. The median time in days is written between two designated lumbar punctures.

Pleocytosis >30 days after treatment initiation was found in 17/93 (18.3%) patients with a second LP and 4/25 (16.0%) patients with a third LP. The subsequent LPs were performed due to no symptomatic improvement ($n = 8$), new onset of symptoms ($n = 3$) or as part of routine follow-up ($n = 8$), (see Supplementary Material 3). In five patients, the second ($n = 4$) or third ($n = 1$) LP was performed more than six months after antibiotic treatment initiation.

Borrelia-specific antibodies in serum

Despite all patients having serum samples analysed as part of measuring the Bb-AI, a specific S-*Borrelia* antibody result was only available in the chart in 533 of the patients. Of those patients, 116 were positive for S-*Borrelia* IgM, 135 for S-*Borrelia* IgG and 207 for S-*Borrelia* IgM+IgG. The median delay from onset of neurological symptoms to blood sampling was 25 days (IQR 14–61 days).

Seventy-five patients (14.1%) with positive Bb-AI were negative for both S-*Borrelia* IgM and IgG, and their median sampling delay was 21 days (IQR 8 – 94 days). CSF pleocytosis was found in 52 (72.0%) of these 75 patients, and there were significantly fewer patients in the Bb-AI IgM-group without pleocytosis ($n = 15/26$) compared with the IgG-group ($n = 5/31$) and IgM+IgG-group ($n = 1/18$), $P<0.001$. Patients with isolated positive S-*Borrelia* IgM had a significantly shorter delay from symptom onset to serologic analysis (15 days, IQR 8–24 days) compared to patients with isolated positive S-*Borrelia* IgG (34 days, IQR 15–103 days) or IgM+IgG (30 days, IQR 20–63 days), $P<0.001$ (see Supplementary Material 4).

Discussion

The primary finding of this study was the lack of correlation between disease duration and the presence of *Bb* IgM or IgG antibodies in the CSF.

We also show that most patients with Bb-AI IgM or IgG antibodies in the CSF continued to have the same Bb-AI over time. The most pronounced examples were two patients who had pos-

itive Bb-AI IgM in three subsequent LPs spanning more than five years but did not produce *Bb* IgG antibodies. Our findings show that the classical pattern found in blood serology in most infections (where initial IgM production is followed by subsequent IgG production) cannot be extended to the interpretation of Bb-AI in CSF [7]. Only a handful of studies with few patients included have looked at symptom duration and the presence of Bb-AI IgM or IgG, and they have produced contradictory results [6, 11-13]. One study that looked solely at Bb-AI IgM hypothesised that Bb-AI IgM may be important for sensitivity in early LNB [14]. Our results do not support this conclusion, based on the many patients with continuous IgM positivity for months to years after symptom onset.

Our study included LNB patients with positive Bb-AI and relevant neurological symptoms, including fifty-seven patients without pleocytosis. When reviewing the medical charts of these 57 patients, a plausible explanation for the absence of pleocytosis was found for most patients where the LP had been performed either at a very early or late stage of the disease, after completed antibiotic treatment or in immunosuppressed patients [11, 15-17]. The absence of pleocytosis could not be explained in 14 patients, however, and we cannot exclude that the positive Bb-AI in these patients represented prior LNB infections with residual symptoms [1, 4, 6]. To ensure an unselected cohort of patients reflecting what we see in clinical practice, we chose not to exclude these patients. This decision was also based on the finding that exclusion of these patients did not alter the lack of correlation between symptom duration and type of antibodies found. We found a significantly larger sub-group of patients with a positive Bb-AI IgM and no *Bb* antibodies in serum to lack pleocytosis compared with the two other groups. This sub-group should be studied in further detail in the future.

Pleocytosis was still present in five patients after six months. While one study found pleocytosis in half the patients three months after treatment initiation [11], other studies have suggested normalization within six months of completed antibiotic treatment in LNB [18, 19]. In the current study, we found a plausible explanation for all five patients with continuous pleocytosis: three had nearly normalised leukocyte count ($<10 \times 10^6$ cells/L) six months after antibiotic treatment, and in two patients the pleocytosis could have been related to a new disease (varicella zoster encephalitis and multiple sclerosis, respectively).

Only nineteen patients had reverted to a negative Bb-AI in the second or third LP. Theoretically, the Bb-AI negative patients could have had an increased S-*Borrelia* titre, leading to a negative Bb-AI, but this was not found. Instead, the Bb-AI negative patients tended to have a decreased OD_{CSF} upon re-examination, with a concomitant reduction of OD_{serum}. Only one patient had increased OD in both CSF and serum. The majority of patients with repeated LPs had continuous positive Bb-AIs over time, underlining that a positive Bb-AI cannot be used to monitor active disease. For monitoring treatment effect, the chemokine CXCL13 has been shown to decline rapidly after relevant antibiotic treatment in LNB patients [20, 21].

To our knowledge, there are no data available on IgM versus IgG type of intrathecal *Bb* antibodies in relation to symptom presentation in LNB. In children, the most common symptoms of LNB are cranial nerve palsy and meningitis [22]. As this is well-known among physicians, we expected a shorter diagnostic delay in children compared to adults. Among all LNB patients, the IgM+IgG-group most often presented with cranial nerve palsy, while patients in the IgG-group more frequently had cognitive symptoms than patients in the IgM-group and more had sensibility disturbances compared with the IgM-group and IgM+IgG-group. We did not find a significantly higher frequency of fever in the IgM-group, which we would have expected if the intrathecal *Bb* antibody production had followed the pattern found in most other infections.

The finding of 14% of patients without *Bb* antibodies in serum at time of positive Bb-AI underlines the importance of performing an LP in all patients suspected of LNB.

The occurrence of sequelae (28.7%) was in accordance with previous studies [23], and there were no differences between the three antibody groups. As there is a well-established correlation between risk of sequelae in LNB and time from symptom onset to treatment, these results substantiate our hypothesis that the early immune response with IgM production followed later by IgG production is not reflected in intrathecal antibody production of LNB patients. Considering the limited knowledge of the association between *Bb* antibody production in CSF and the clinical picture, further corroboration of the results is needed.

A strength of the current study is the large sample size of >500 LNB patients from a well-defined geographical area. Throughout the whole study period, the same assay was used to determine the presence of intrathecal production of *Bb* antibodies. Hence, the Bb-AI is comparable for all included patients. In regards to generalisability, however, it should be noted that we used a *Bb* IgG/IgM capture assay that compared fractions of *Bb* antibodies in CSF and serum. Most other intrathecal assays compare the concentration of *Bb* antibodies in the two compartments [10]. In addition, the IDEIA assay uses purified native flagellar protein as antigen, as this is generally included in the CSF immune response [10]. Other assays use a broader range of antigens, but nevertheless, published results have shown the same level of sensitivity and specificity between the IDEIA and other Bb-AI assays [24].

The retrospective nature of the current gives some limitations. Patients were included based on time of diagnosis and not symptom onset, so complete data were not available for all patients. Despite this, few patients had missing data or were lost to follow-up. Time of last hospital contact was not registered, which affects the interpretation of data on sequelae. Furthermore, as only patients who had evidence of intrathecal *Bb* antibody production were included, patients in the early phase of LNB with an initial negative Bb-AI were by default excluded [1, 16, 25]. This may have affected the length of delay found in our study. To strengthen the results found in this study, prospective studies with repeated lumbar punctures examining *Bb* IgM and IgG index at fixed time points could be conducted.

In conclusion, we found that the intrathecal *Bb* antibody production in LNB does not follow the well-known pattern found in blood serology for most other infections with an initial IgM response followed by an IgG response. LNB patients continue to express the same intrathecally produced antibodies throughout their disease course and seldom convert. Based on our results, physicians diagnosing patients with LNB should not base their interpretation of stage of disease on the type of *Bb* antibodies found in the CSF. The correlation between Bb-AI results and the clinical presentation of LNB needs further evaluation.

Authors' contributions

Conception and design: S.S., F.C.K. Acquisition of data: F.C.K. Statistical analysis: I.K. Interpretation of data: I.K., S.S., T.G.R., F.C.K. Drafting the article: I.K., S.S, T.G.R., F.C.K. All authors read and approved the final version of the manuscript.

Data availability

The dataset generated for the cohort study is not publicly available due to the Danish Data Protection Law. It is available from the corresponding author upon reasonable request.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Acknowledgements

We thank Claire Gudex associate professor at the Faculty of Health Sciences, University of Southern Denmark for English proofreading of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.08.045.

References

[1]. Stanek G, et al. Lyme borreliosis. *Lancet* 2012;**379**(9814):461–73.
[2]. Halperin JJ. Neurologic manifestations of lyme disease. *Curr. Infect. Dis. Rep.* 2011;**13**(4):360–6.
[3]. Mygland A, et al. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. *Eur. J. Neurol.* 2010;**17**(1):8–16 e1-4.
[4]. Djukic M, et al. Cerebrospinal fluid findings in adults with acute Lyme neuroborreliosis. *J. Neurol.* 2012;**259**(4):630–6.
[5]. Dessau RB, et al. To test or not to test? Laboratory support for the diagnosis of Lyme borreliosis: a position paper of ESGBOR, the ESCMID study group for Lyme borreliosis. *Clin. Microbiol. Infect.* 2018;**24**(2):118–24.
[6]. Hammers-Berggren S, et al. Borrelia burgdorferi-specific intrathecal antibody production in neuroborreliosis: a follow-up study. *Neurology* 1993;**43**(1):169–75.
[7]. Bennett John E DR BMJ. *Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th Edition edn. Elsevier Saunders; 2015.
[8]. Knudtzen FC, et al. Characteristics and Clinical Outcome of Lyme Neuroborreliosis in a High Endemic Area, 1995-2014: a Retrospective Cohort Study in Denmark. *Clin. Infect. Dis.* 2017;**65**(9):1489–95.
[9]. Dessau, R.B., J.M.; Hansen, K.; Lebech, A.M.; Sellebjerg, F.; Skarphedinsson, S.; Østergaard, C.. *Lyme Borreliose - Klinik, diagnostik og behandling i Danmark*. 2014 [cited 2022 22.02]; 2. edition:Available from: https://dskm.dk/onewebmedia/Borrelia%20klaringsrapport%202.udgave%202014.pdf.
[10]. 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**(2):197–205.
[11]. Ogrinc K, et al. Course and Outcome of Early European Lyme Neuroborreliosis (Bannwarth Syndrome): clinical and Laboratory Findings. *Clin. Infect. Dis.* 2016;**63**(3):346–53.
[12]. Pierer K, et al. Is IgM of diagnostic value in case of delayed intrathecal production of IgG antibodies? *Wien. Klin. Wochenschr.* 1999;**111**(22):957–60 -23.
[13]. Kaiser R. Variable CSF findings in early and late Lyme neuroborreliosis: a follow-up study in 47 patients. *J. Neurol.* 1994;**242**(1):26–36.
[14]. Hillerdal H, Henningsson AJ. Serodiagnosis of Lyme borreliosis-is IgM in serum more harmful than helpful? *Eur. J. Clin. Microbiol. Infect. Dis.* 2021.
[15]. Tveitnes D, Øymar K, Natås O. Laboratory data in children with Lyme neuroborreliosis, relation to clinical presentation and duration of symptoms. *Scand. J. Infect. Dis.* 2009;**41**(5):355–62.
[16]. Nordberg CL, et al. Lyme neuroborreliosis in adults: a nationwide prospective cohort study. *Ticks Tick Borne Dis.* 2020;**11**(4):101411.
[17]. Christen HJ, et al. Epidemiology and clinical manifestations of Lyme borreliosis in childhood. A prospective multicentre study with special regard to neuroborreliosis. *Acta Paediatr. Suppl.* 1993;**386**:1–75.
[18]. Ljøstad U, et al. *Oral doxycycline* versus *intravenous ceftriaxone for European Lyme neuroborreliosis: a multicentre, non-inferiority, double-blind, randomised trial*. *Lancet Neurol.* 2008;**7**(8):690–5.
[19]. Pfister HW, Rupprecht TA. Clinical aspects of neuroborreliosis and post-Lyme disease syndrome in adult patients. *Int. J. Med. Microbiol.* 2006;**296**(40):11–16 **Suppl**.
[20]. Hytonen J, et al. CXCL13 and neopterin concentrations in cerebrospinal fluid of patients with Lyme neuroborreliosis and other diseases that cause neuroinflammation. *J. Neuroinflammation* 2014;**11**:103.
[21]. Knudtzen FC, et al. The predictive value of CXCL13 in suspected Lyme neuroborreliosis: a retrospective cross-sectional study. *Eur. J. Clin. Microbiol. Infect. Dis.* 2020;**39**(8):1461–70.
[22]. Øymar K, Tveitnes D. Clinical characteristics of childhood Lyme neuroborreliosis in an endemic area of northern Europe. *Scand. J. Infect. Dis.* 2009;**41**(2):88–94.
[23]. Berglund J, et al. 5-y Follow-up study of patients with neuroborreliosis. *Scand. J. Infect. Dis.* 2002;**34**(6):421–5.
[24]. Henningsson AJ, et al. Laboratory diagnosis of Lyme neuroborreliosis: a comparison of three CSF anti-Borrelia antibody assays. *Eur. J. Clin. Microbiol. Infect. Dis.* 2014;**33**(5):797–803.
[25]. Ljøstad U, Skarpaas T, Mygland A. Clinical usefulness of intrathecal antibody testing in acute Lyme neuroborreliosis. *Eur. J. Neurol.* 2007;**14**(8):873–6.