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Risk of Neurological Disorders in Patients with European Lyme Neuroborreliosis

A Nationwide, Population-based Cohort Study

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Risk of neurological disorders in patients with European Lyme neuroborreliosis. A nationwide population-based cohort study.

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Short summary:

We examined the risk of neurological disorders in patients with Lyme Neuroborreliosis. No increased long-term risk of neurological diseases was observed. An increased short-term risk of epilepsy and Guillain-Barré syndrome observed is likely to be caused by diagnostic bias.

Part of the results in this paper has previously been presented as a late breaker poster at the 29th European Congress of Clinical Microbiology & Infectious Diseases in Amsterdam, Netherlands in April 2019.

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ABSTRACT

Background

Lyme neuroborreliosis (LNB) caused by the tick-borne spirochetes of the *Borrelia burgdorferi* sensu lato species complex has been suggested to be associated with a range of neurological disorders. In a nationwide population-based cohort-study we examined the association between LNB and dementia, Alzheimer's disease, Parkinson's disease, motor neuron disease, epilepsy and Guillain-Barré syndrome.

Methods

We used national registers to identify all Danish residents diagnosed during 1986-2016 with LNB (n=2,067) and a gender and age matched comparison cohort from the general population (n=20,670), and calculated risk estimates and hazard ratios (HR).

Results

We observed no long-term increased risk of dementia, Alzheimer's disease, Parkinson's disease, motor neuron diseases or epilepsy. However, within the first year eight (0.4%) of the LNB patients developed epilepsy compared with 20 (0.1%) of the comparison cohort (difference 0.3%, 95% CI: 0.02% to 0.6%). In the LNB group 11 (0.5%) patients were diagnosed with Guillain-Barré syndrome within the first year after LNB diagnosis compared with 0 (0.0%) in the comparison cohort. After the first year, the risk of Guillain-Barré was not increased.

Conclusion

LNB patients did not have increased long-term risk of dementia, Alzheimer's disease, Parkinson's disease, motor neuron diseases, epilepsy or Guillain-Barré. Although absolute risk is low, LNB patients might have an increased short-term risk of epilepsy and Guillain-Barré syndrome.

Keywords: European Lyme Neuroborreliosis; Long-Term-Risk; Neurodegenerative Disorders; Borrelia burgdorferi; Nation-wide population-based cohort study

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INTRODUCTION

Lyme neuroborreliosis (LNB) designates the nervous system disorder caused by tick-borne spirochetes of the *Borrelia burgdorferi sensu lato species complex*. In Europe LNB is characterized by a subacute painful radiculoneuritis, peripheral motor deficits and lymphocytic cerebrospinal fluid (CSF) inflammation. Third stage LNB compromise less than 1–2% of all LNB patients and is defined as a progressing meningoencephalomyelitis[1]. The diagnostic criteria and antibiotic treatment of both early and late LNB are well established, but the frequency and spectrum of residual symptoms in patients with LNB is still a matter of debate[2]. Possible associations have been suggested between LNB and neurological disorders, such as dementia, Alzheimer's disease, Parkinson's disease, motor neuron disease, epilepsy and Guillain-Barré syndrome[3]. All associations are stated as rare and the hypothesized underlying mechanisms include both a direct causal effect of active infection and sequelae of LNB either treated or untreated. However, these studies are often confined to small or selected study populations at single centers without adequate comparison cohorts and limited follow-up.

In a recent nationwide population-based cohort study of LNB patients, we have demonstrated that a verified diagnosis of LNB had no substantial impact on long-term survival, health, social functioning, or education[4]. Specifically, there was no increased risk of multiple sclerosis in LNB patients compared with the general population[4]. In the current study, we used the same cohort of LNB patients and a comparison cohort from the general population to examine if there is an association between LNB and dementia, Alzheimer's disease, Parkinson's disease, motor neuron disease, epilepsy and Guillain-Barré syndrome.

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METHODS

Setting

Denmark has a population of approximately 5,8 million individuals. Tax-supported health care is provided free of charge to all Danish residents[5].

Study populations and data sources

We used a previously described LNB patient cohort to conduct a nationwide, population-based cohort study[4]. We identified all Danish residents who had an intrathecal *B. burgdorferi* antibody IgG and/or IgM index performed during the period 1 January 1985 to 31 December 2015. We extracted all with a positive intrathecal antibody index and Danish residency at study inclusion from this population. Next, we excluded all who were not registered with a diagnosis of LNB in the Danish National Patient Registry (DNPR) within one year after study inclusion or had contact with a department of neurology earlier than one year before study inclusion. We used the unique 10-digit personal identification number assigned to all Danish residents at birth or upon immigration to link data with the Danish Civil Registration System, the DNPR and housing statistics from Statistics Denmark[4], [5]. Diagnoses in DNPR are coded by the attending physician according to the International Classification of Diseases, Eighth Revision (ICD-8) until 31 December 1993 and thereafter by the Tenth Revision (ICD-10)[6]. From the Danish Civil Registration System and DNPR, we identified the comparison cohort consisting of 10 individuals from the general population for each LNB patient, who had the same sex and date of birth, were Danish residents, were living in Denmark at time of study inclusion and had no contact with a department of neurology earlier than one year before study inclusion. Inclusion and exclusion criteria of the total study population has previously been described in detail [4].

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Statistical analysis

From the DNPR, we extracted clinical diagnoses of dementia (F00-F03), Alzheimer's disease (F00), Parkinson's Disease (G20-G21), motor neuron diseases including ALS (G12.2), epilepsy (G40-F41) and Guillain-Barré syndrome (G61.0). We extracted information on nursing home residency from Statistics Denmark, as this could be a surrogate marker of subclinical dementia or neurodegenerative disorder in general. Study inclusion was the date of lumbar puncture for LNB patients. Individuals from the comparison cohort were assigned the same date of study inclusion as the LNB patient they were matched to. Individuals in both the LNB and comparison cohorts were excluded from the statistical analyses if they were diagnosed with the disease of interest (the outcome) more than 3 months before study inclusion. We calculated time from date of study inclusion to 1 March 2016, death, emigration, loss to follow-up, or event of interest, whichever came first. If an outcome was diagnosed for the first time within three months before study inclusion, the date of diagnosis of the outcome was set to the day after study inclusion. This was done, as the outcome may occur before lumbar puncture, even if related to the LNB episode[2]. Sensitivity analyses were performed, in which all persons who were diagnosed with the event of interest before study inclusion were excluded. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated using Cox regression as a measure of relative risk. As our initial analysis showed that there was not a constant hazard over time, we only calculated hazard ratios for the long-term follow-up (>= 12 months). Cumulative incidence curves were computed using cumulative incidence function, in which death was considered competing risk[7]. We calculated 1-year risks of each neurological disorder for both LNB patients and members of the comparison cohort by use of the cumulative incidence function [4]. For the patient and comparison cohorts, we also ascertained the proportion of persons who had inpatient and/or outpatient contacts associated with each of the neurological disorders of interest in yearly intervals starting at the latest of 3 months before study inclusion, birth, immigration, or start-up date of the registry recording the outcome of interest, up until 10 years after study inclusion, 1 March 2016, death, emigration, loss to follow-up, whichever came first. These proportions were calculated as measures of disease burden.

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Finally, for Guillain-Barré syndrome, we also calculated estimates of proportions of inpatient visit per week in the first year before and after study inclusion.

SPSS Statistics, version 24 (SPSS, Inc., Chicago, Illinois) and R version 3.5.1 was used for all analysis [8].

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RESULTS

A total of 2,067 LNB patients and 20,670 members of the comparison cohort were identified for this study. Median age was 46 years (interquartile range [IQR]: 12 years to 62 years) and 43.7% were women.

Long-term risks of dementia, Alzheimer's disease, Parkinson's disease, motor neuron diseases including ALS and nursing home residency

We observed no increased long-term risk of Alzheimer's disease, Parkinson's disease, motor neuron diseases or nursing home residency for LNB patients compared with members of the comparison cohort (Table 1 and Figure 1). Further the yearly proportion of LNB patients who had hospital contact related to these disorders were not increased compared with members of the comparison cohort (Supplementary Figure 1). The sensitivity analyses were consistent with these results (data not shown).

Long-term risk of epilepsy in LNB patients

We observed no increased long-term risk of epilepsy (HR 1.31, 95% CI: 0.88 to 1.96). However, within the first year eight LNB patients compared with 20 of the comparison cohort developed epilepsy. The 1-year risk of epilepsy for LNB patients was 0.39% compared with 0.10% for the comparison cohort (difference 0.29%, 95% CI: 0.02% to 0.56%). The proportion of LNB patients, who had a hospital contact with a diagnosis of epilepsy was slightly increased up to ten years after the LNB diagnosis (Supplementary Figure 1E). In the sensitivity analyses, in which we excluded LNB patients diagnosed with epilepsy in the period of three months before LNB diagnosis, the difference in 1-year risk of epilepsy was 0.13 (-0.07 to 0.32) – except from that, the sensitivity analyses did not change the remaining estimates substantially (Data not shown).

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Long-term risk of Guillain-Barré syndrome in LNB patients

Thirteen LNB patients and seven members of the comparison cohort were diagnosed with Guillain-Barré syndrome during the entire follow-up (Figure 1F). During the first year of follow-up 11 LNB patients and 0 members of the comparison cohort were diagnosed with Guillain-Barré. The 1-year risk of Guillain-Barré syndrome for LNB patients was 0.53% compared with 0.00% for the comparison cohort (difference 0.53%, 95% CI: 0.22% to 0.85%). After the first year additional two LNB patients and seven members of the comparison cohort developed Guillain-Barré syndrome (HR 2.84, 95% CI: 0.59 to 13.69). The proportion of persons who had a hospital contact with a diagnosis of Guillain-Barré syndrome was increased in the LNB patient cohort in the year of inclusion, but thereafter waned (Supplementary Figure 1F and Supplementary Figure 2).

The results of the sensitivity analysis were essentially identical (data not shown).

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DISCUSSION

In this nationwide, population-based cohort study, we observed no increased long-term risk of dementia, Alzheimer's disease, Parkinson's disease, motor neuron disease, epilepsy, Guillain-Barré syndrome or nursing home residency among LNB patients compared with a comparison cohort consisting of 10 gender and age matched individuals from the general population. However, we did observe an increased short-term risk of Guillain-Barré syndrome and epilepsy, although this increase was small in absolute terms.

Strength and limitations

Study strengths are the large sample size, length and completeness of follow-up and the use of national population-based registers limiting selection bias and allowing comparisons with a matched comparison cohort. Limitations include lack of access to information on CSF-cell-count, stage of LNB, initial neurological symptoms and antibiotic therapy. However, a rigorous case definition of LNB patients requiring both a positive intrathecal antibody index and a diagnosis code of Lyme borreliosis in the DNPR offers reassurance that the clinical condition was consistent with LNB. The diagnoses of epilepsy and Guillain-Barré syndrome have been shown to have high validity in the DNPR[9], [10], and the risk of misdiagnosis is minimal with regards to these diagnoses. It is a potential limitation of our study that we did not match individuals in the comparison cohort by area of residence. By matching on age and date of birth, however, we believe that most of the potential confounding conveyed by area of residence, has been accounted for.

Discussion of our own results and comparison with other studies

A possible association has been suggested between LNB and dementia, Alzheimer's disease, Parkinson's disease and motor neuron diseases[11]–[14]. However unclear or inadequate case definitions of LNB might have hampered these studies as the magnitude and spectrum of "residual symptoms" has been demonstrated to increase with less rigorous case definitions [15]. Further, these studies are of small size

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[3], [11], [12], hampered by selection bias [11] or with no adequate comparison cohort [11], [14]. Despite the long-term follow-up in our large cohort of LNB patients, we were not able to demonstrate any increased risk of dementia, Alzheimer's disease, Parkinson's disease and motor neuron disease, which is consistent with a geoepidemiology study from the US in which there was no association between the geographical distribution of Lyme disease and the geographical distribution of these neurological disorders[16]. In fact, LNB patients might be subject to detection bias inferred by the diagnostic work-up during and after diagnosis thus increasing the likelihood of diagnosing subclinical dementia, Alzheimer's disease, Parkinson's disease and motor neuron disease [17]. Therefore, it is reassuring that no increased risks of these diseases were demonstrated in our study. Finally, as these diseases initially can be subclinical, it is encouraging that we did not demonstrate any increased risk of nursing home residency among LNB patients, which could otherwise be regarded as a surrogate marker of neurodegenerative disorders. Taken together, these findings argue against any association of dementia, Alzheimer's dementia, Parkinson's disease and motor neuron disease with LNB. It has been proposed, that late LNB can cause dementia-like symptoms [3]. As these dementia-like symptoms are likely to be recorded as dementia in DNPR, this phenomenon is probably small, as we did not observe any increased risk of dementia in our study.

We did not find an increased long-term risk of epilepsy for LNB patients compared with the general population. However, LNB patients had significant more events of epilepsy within the first year of LNB diagnosis compared with the comparison cohort. It is likely that the diagnostic work up of first-time seizures might reveal a subclinical LNB, that had resolved spontaneously but left the patient positive for *B. burgdorferi* antibody index[18]. This hypothesis is partly supported by the fact that the difference in 1-year risk of epilepsy was no longer statistically significant in the sensitivity analyses where we excluded persons diagnosed with epilepsy in the 3 months period leading up to LNB diagnosis. Certainly, LNB can manifest as epilepsy on rare occasions[18], [19], although much less often than with other infections of CNS[20]. Nonetheless, it is important, that the proportion of LNB patients with a hospital contact related to epilepsy

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was low and did not increase over time. Further, the LNB patients were not at increased risk of being diagnosed with epilepsy from the second year and onwards. Taken together, epilepsy seems to be a minor problem in LNB patients.

We found an increased risk of Guillain-Barré syndrome among LNB patients compared with the general population comparison cohort in the first weeks of follow-up, although in absolute numbers Guillain-Barré syndrome was very infrequent. The very short time span from LNB diagnosis to Guillain-Barré syndrome is in line with the finding that Guillain-Barré syndrome often develops within one month after infection[21]. This agrees with case-reports of Lyme borreliosis causing or mimicking Guillain-Barré syndrome[22], [23]. These case-reports, however, do not fulfill diagnostic criteria of LNB as they only rely on elevated serum *B.burgdorferi* antibodies and not intrathecal antibody index. Guillain-Barré syndrome is well known to be caused by bacterial and viral organisms, especially *Campylobacter jejuni* [21]. The molecular basis for this syndrome is likely to be due to antibody-mediated attack on the myelin and to some extent the axolemma. Whether this autoimmune reaction develops probably depends on pathogen and patient characteristics [21]. It is difficult from our data to determine whether LNB starts the autoimmune response of Guillain-Barré syndrome or LNB mimics the symptoms of Guillain-Barré syndrome. Finally, the diagnosis of LNB could be a result from diagnostic bias, as patients suffering from Guillain-Barré syndrome are likely to have a lumbar puncture and various CSF test including *B.burgdorferi* intrathecal antibody index performed. A positive intrathecal antibody test might be due to persistent *B. burgdorferi* antibody index following an earlier undiagnosed LNB [24].

We conclude, that LBN does not lead to substantially increased risk of neurological disorders among LNB patients. A short-term increased risk of Guillain-Barré syndrome and epilepsy observed among LNB patients is likely to be explained by diagnostic bias. Our findings serve to reassure patients of a low risk of neurological diseases after an episode of LNB.

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NOTES

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Potential conflicts of interest: Dr. Dessau reports personal fees from Advisory board meeting 2018, Roche Diagnostics, outside the submitted work; and Shares Novo Nordisk (part of pension scheme). Dr. Benfield reports grants from Pfizer, grants from Novo Nordisk Foundation, grants from Simonsen Foundation, grants from GSK, personal fees from Pfizer, personal fees from Boehringer Ingelheim, personal fees from Gilead, outside the submitted work. Dr. Hansen reports royalties from ThermoFisher, outside the submitted work. All other authors: No reported conflicts of interest.

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TABLE 1. Risk of neurological disorders in Lyme neuroborreliosis patients compared with members of the comparison cohort

Diagnosis (ICD-10)	Follow-up period							
	0-1 years					1+ years		
	No of event in LNB patients	No of event in the comparison cohort	1-year risk (%) in LNB* patients	1-year risk (%) in comparison cohort	Difference in 1-year risk (%) (95% CI)	No of event in LNB patients	No of event in the comparison cohort	HR** (95% CI)
Dementia	5	12	0.24	0.06	0.18 (-0.031 to 0.40)	33	326	0.89 (0.60 to 1.31)
Alzheimer's disease	0	3	0.00	0.01	-0.01 (-0.03 to 0.00)	12	108	1.14 (0.62 to 2.06)
Parkinson's disease	1	1	0.05	0.00	0.04 (-0.05 to 0.14)	7	76	0.79 (0.35 to 1.82)
Motor neuron disease	0	3	0.00	0.01	-0.01 (-0.03 to 0.00)	3	19	1.86 (0.54 to 6.37)
Epilepsy	8	20	0.39	0.10	0.29 (0.02 to 0.56)	35	255	1.31 (0.88 to 1.96)
Guillain-Barré syndrome	11	0	0.53	0.00	0.53 (0.22 to 0.85)	13	7	2.84 (0.59 to 13.69)
Nursing home residency	2	21	0.10	0.08	0.01 (-0.13 to 0.16)	21	304	0.67 (0.42 to 1.06)

***** LNB; Lyme Neuroborreliosis, ******HR; Hazard Ratio

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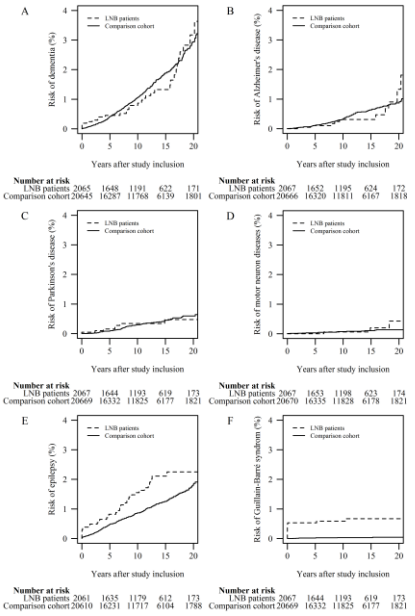
Figure 1. Cumulative risk of neurological diseases in Lyme neuroborreliosis patients compared with members of the comparison cohort.



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