

Clinical and epidemiological features of Lyme neuroborreliosis in adults and factors associated with polyradiculitis, facial palsy and encephalitis or myelitis

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Abstract

The clinical course of Lyme neuroborreliosis (LNB) is highly variable. Delayed diagnosis and treatment still remain actual challenges. Moreover, there is a lack of studies analyzing the factors associated with different LNB syndromes. We aimed to analyze clinical and epidemiological features of LNB in hospitalized adults. A retrospective study was performed in the years 2010–2021. A total of 103 patients were involved in the study, 100 with early, and three with late LNB. Patients with early LNB most often presented polyradiculitis (75/100, (75%)), which was also the most common initial neurological syndrome. Peripheral facial palsy was diagnosed in 53/100 (53%) patients, in 16/53 (30.2%) cases both facial nerves were affected. Encephalitis or myelitis was diagnosed in 14% of patients with LNB. A total of 76/103 (73.8%) patients were discharged with residual symptoms or signs. One patient presenting encephalomyelitis died because of bacterial complications. We found that female sex and untreated erythema migrans (EM) were associated with the development of isolated polyradiculitis, the absence of EM was associated with the development of peripheral facial palsy, and a fever of $\geq 38^{\circ}\text{C}$ and pleocytosis of $\geq 300 \times 10^6/\text{l}$ were associated with encephalitis or myelitis in patients with early LNB.

Introduction

Lyme Borreliosis (LB) is the most common tick-borne disease in Europe, including Lithuania. In Europe, 65 500 people are affected by this disease annually¹. The incidence is the highest in Scandinavian and the Baltic states in northern Europe, and in Austria, Czechia, Germany, and Slovenia in central Europe². In Lithuania, a significant rise of morbidity was observed in years 2010–2021, and incidence rate varied between 63.7 and 117.8 cases per 100 000 inhabitants³.

LB is a zoonosis transmitted by ticks and caused by *Borrelia (B.) burgdorferi sensu lato* (s.l.) spirochete complex^{1,4}. *B. burgdorferi* s.l. is classified into 3 main genospecies: *B. burgdorferi sensu stricto* (s.s.), *B. afzelii*, *B. garinii*.

LB is a multisystem, multistage disease. Erythema migrans (EM) is the most common manifestation of LB. Early Lyme neuroborreliosis (LNB) is the second most frequent clinical manifestation in Europe, which occurs in 10–15% of all LB cases⁵. The clinical course of LNB is highly variable. Any part of the nervous system may be involved, but the disease usually manifests as lymphocytic meningitis, meningopolyradiculitis, and/or cranial neuritis¹. Encephalitis and myelitis are the most severe forms but occur rarely¹. It is important to diagnose this infectious disease as early as possible in order to introduce appropriate treatment before it results in axonal loss⁶ or other neurological deficits that impair the patients' quality of life and requires long rehabilitation. Although the clinical manifestation of LNB is relatively well studied, factors associated with various LNB syndromes are still insufficiently analyzed; delayed diagnosis and treatment remain actual challenges as well.

The aim of this study was to analyze clinical and epidemiological features of LNB in hospitalized adults, and to identify the factors associated with the development of polyradiculitis, peripheral facial palsy, and

encephalitis or myelitis.

Results

Epidemiological and demographic data

The study involved 103 patients. The possible LNB (PLNB) was diagnosed in 8/103 (7.8%) patients, and 5 of them had the presence of EM (Table 1). A total of 34/103 patients (33%) had presence or reliable history of recent EM within 120 days before the onset of the neurological symptoms or signs, and 31/34 (91%) of these cases were untreated.

The most common co-morbidities were arterial hypertension (39.8%) and diabetes (6.8%). Other concomitant diseases were cancer (3.8%), coronary heart disease (3.8%), and chronic kidney disease (2.9%).

The highest number of LNB cases occurred in July (Fig. 1). Most often, patients became infected in their living area – the city of Vilnius (46/103 patients, 44.7%) and the Vilnius region (16/103 patients, 15.5%).

Clinical presentation

The majority of patients (100/103, (97.1%)) were diagnosed with early LNB. Patients with early LNB most often presented polyradiculitis (75/100 cases, (75%)) (Fig. 2). The radicular pain was the most frequent first neurological symptom (Table 1). The most common location of radicular pain was lower back (36/75 cases, (48%)), followed by shoulder girdle (22/75 cases, (29.3%)). Legs and chest were affected in 20/75 cases each (26.7%), arms in 7/75 cases (9.3%), neck in 14/75 cases (18.7%). A total of 23/75 (30.7%) patients with polyradiculitis had the presence or reliable history of recent EM, while 22 cases were untreated.

Cranial neuropathies were diagnosed in 56/100 cases (56%) (Fig. 2) and were reported less often in patients with EM compared to patients without the history of EM ((13/34 (38.2%) vs 43/66 (65.2%), $p = 0.010$).

Peripheral facial palsy was diagnosed in 53/100 patients (53%) (Fig. 2); in 16/53 cases (30.2%) both facial nerves were affected. The median time from unilateral to bilateral peripheral facial palsy was 3 days (IQR 0–5, min 0, max 10, $n = 15$).

Nine patients (9%) presented symptoms and signs of encephalitis (Fig. 2). Ataxia was the most prevalent encephalitis symptom, appearing in seven cases; in one case, it was so severe that the patient was unable to walk for a month. Memory disorders, facial myoclonus, writing problems, and dysphagia were all reported with frequency of 1/100 cases (1%) each. A total of 7/9 patients had a fever median 38.5°C ((37.8-39); min 37.4°C – max 39°C). Two patients had a two-wave fever.

Myelitis was diagnosed in two patients with early LNB. A 22-year-old patient presented spastic paraparesis of legs, sensory impairment, urinary retention, and left peripheral facial palsy. The patient had no signs of encephalitis and no abnormalities in head magnetic resonance imaging (MRI). The patient had a history of untreated EM within 14 days prior to the onset of neurologic symptoms. At the beginning of the disease, intrathecal synthesis of *B. burgdorferi* s.l. antibodies, as well as *B. burgdorferi* s.l. antibodies in the serum were not detected, but inflammatory changes were found in the cerebrospinal fluid (CSF). After 2 weeks, intrathecal synthesis of *B. burgdorferi* s.l. IgM was detected, but antibodies were not detected in serum. *B. burgdorferi* s.l. IgM antibodies were detected 3 weeks after the onset of the illness. An 88-year-old patient presented fever and paresis of left leg. After 10 days, the patient developed stupor, lower paraparesis, accompanied by sensory loss and urinary retention. The patient was previously healthy and active, had no history of EM and tick bite, but often visited forests.

Univariable logistic regression showed that female sex and untreated EM were associated with increased odds ratio of having isolated polyradiculitis in patients with early LNB. In multivariable regression, female sex and untreated EM remained statistically significant predictors of isolated polyradiculitis (Table 2).

Univariable regression revealed that age, male sex, and absence of EM were associated with increased odds ratio for the development of peripheral facial palsy in patients with early LNB. In multivariable regression, the absence of EM remained statistically significant, associated with 2.84 (95% CI 1.15–7.00) fold increased odds ratio for developing facial palsy (Table 2).

A fever of $\geq 38^{\circ}\text{C}$ and pleocytosis of $\geq 300 \times 10^6/\text{l}$ predicted encephalitis and/or myelitis in patients with early LNB (Table 2).

Late LNB was diagnosed in 3/103 patients (2.9%). Two of them presented with encephalitis, and one with encephalomyelitis. A 66-year-old patient with encephalitis presented dizziness, cerebellar ataxia, diplopia, and dysphagia. The patient had a history of self-limiting peripheral facial palsy. A 42-year-old patient presented headache, cerebellar ataxia, and diplopia. A 71-year-old patient with encephalomyelitis presented fever, headache, tremor, signs of vestibulocochlear neuropathy, and signs of myelitis.

Laboratory and instrumental findings

There were no significant abnormalities in hematology tests, C reactive protein (CRP), or erythrocyte sedimentation rate (ESR) (Table 3). CSF analysis was performed in all LNB patients. All patients with early LNB had elevated cell count in CSF (median $112 \times 10^6/\text{l}$, minimum $12 \times 10^6/\text{l}$ – maximum $867 \times 10^6/\text{l}$) (Table 4). The intrathecal synthesis of neither IgM, nor IgG *B. burgdorferi* s. l. was detected in eight patients whose cerebrospinal fluid was examined less than 8 weeks after the onset of the disease. Higher pleocytosis was observed in patients with encephalitis and/or myelitis ($p = 0.005$) (Fig. 3).

Head MRI was performed for 9/103 (8.7%) LNB patients, 5/9 (55.6%) scans were abnormal and related to LNB. All patients were presenting encephalitis and had hyperintense T2 signal abnormalities, including small lesions in subcortical and periventricular areas, deep white matter, and cerebellar hemispheres. One

patient showed increased periventricular T2 signal. A case of confluent contrast-enhancing T2 lesions involving basal ganglia, diencephalon, midbrain, and pons is presented in Fig. 4. Cranial nerve contrast enhancement was prominent in four scans and involved oculomotor and facial nerves.

Ten (9.7%) LNB patients underwent spinal MRI. While nine had various abnormalities, only two were related to LNB. Two patients presenting myelitis had non-enhancing T2 hyperintense lesions in upper thoracic spinal cord, one lesion was segmental and involved posterior column, while the other scan showed transverse myelitis extending for three segments. A detailed description of MRI findings is presented in supplementary Table A1 online.

Electrodiagnostic evaluation was performed for 9/103 (8.7%) patients with LNB. Nerve conduction studies (NCS) and/or electromyography (EMG) were performed to determine the severity of peripheral nervous system involvement. The clinically mild facial weakness was confirmed after doing facial nerve NCS with BLINK reflex in three cases. For other patients, NCS was performed for the evaluation of limb weakness. Time from the onset of the first muscle weakness signs to electrodiagnostic evaluation varied from 7 days to 6 months. All patients with limb weakness suffered severe radicular pains before the development of the paresis. For LNB patients with proximal limb weakness, the most common NCS finding was prolonged latencies of F waves – a sign of lesions in proximal parts or roots of the nerve. These findings and clinical features are summarized in supplementary Table A2 online.

Treatment and outcomes

The median duration of hospitalization of LNB patients was 15.7 days ((IQR 10–19), min 1 – max 63). Patients with isolated polyradiculitis were treated in hospital for a shorter period compared to patients with facial palsy (13 (IQR 8.5–15) vs 16 (IQR 11–20), $p = 0.014$ respectively), or patients with encephalitis or myelitis (13 (IQR 8.5–15) vs 20 (IQR 18.5–28.75), $p < 0.001$ respectively) (Fig. 3). The median duration from the onset of symptoms to hospitalization was 20 days (Table 1). Patients with isolated peripheral facial palsy were hospitalized earlier compared to patients with polyradiculitis (median duration from symptom onset to hospitalization 5.5 days, IQR 1.5–7, min 0 – max 14, $n = 10$ vs 24 days, IQR 16–32.5, min 3 – max 63, $n = 69$, $p < 0.001$), as were patients with encephalitis (median 4 days, IQR 2–24, min 1 – max 33, $n = 9$, $p = 0.006$).

All patients with LNB were prescribed intravenous ceftriaxone. A total of seven LNB patients were treated with oral doxycycline 100mg twice a day for 4–21 days before hospitalization, and all of them experienced the failure of treatment. The symptoms of LNB progressed with intravenous ceftriaxone over a period of one week in three patients.

A total of 76/103 (73.8%) LNB patients were discharged with residual neurological symptoms or signs. The most common persisting neurological sign was unresolved peripheral facial palsy (40/103, 38.8%). Other unresolved neurological symptoms and signs were paresis (11/103, 10.7%), radicular pain (12/103, 11.7%), ataxia (3/103, 2.9%), ophthalmoplegia (1/103, 1%), and dizziness (1/103, 1%). One 88-year-old patient with encephalomyelitis died because of bacterial complications.

Discussion

LNB has a variety of clinical manifestations. The results of our study showed that polyradiculitis, reported in 75% of cases, was the most common presentation of early LNB. This was also the first syndrome of LNB described by Garin, Bujadoux and Bannwarth⁷. Patients with Bannwarth syndrome have severe migrating radicular pain, which is not relieved by analgesics. The clinical picture of Bannwarth syndrome is often misinterpreted, and patients go through numerous investigations. In other studies, polyradiculitis was also the most common symptom with a frequency of 66%^{8,9}, and 81%¹⁰. A total of 33% of our patients presented isolated polyradiculitis, which is similar to the study of Schwenkenbecher et al.¹¹ – 25%, but lower than in the study of Nordberg et al.¹² – 45%. Although polyradiculitis was the most common presentation and the most common initial symptom of early LNB, it was not the leading symptom for hospitalization. Patients with polyradiculitis had delayed hospitalization (median duration of symptoms before hospitalization 24 days vs 5.5 days without polyradiculitis, $p < 0.001$). The developing peripheral facial palsy or encephalitic signs were the reasons for hospital admission. One of the most surprising findings was that as much as 91% of EM cases were untreated. It can be said that one third of early LNB cases could have been prevented if EM had been treated. Our results indicate that there is still a need for education of both professionals and the public about the most common symptoms of LB.

Peripheral facial palsy was the second leading manifestation of early LNB observed in 53% of cases in our study. In other studies, the rate of facial palsy was 52%¹⁰, 43%¹¹, 41.3%⁸, and 36.4%¹³. According to our study, the rate of isolated facial palsy is 11%, while in the study of Schwenkenbecher et al.¹¹ it was 16%. Univariable and multivariable regressions revealed that the absence of EM is associated with developing peripheral facial palsy. It is known that *B. afzelii* is associated with skin manifestation and *B. garinii* with nervous system involvement. It is not clear why patients without EM are more likely to develop facial neuropathy; microbiological studies are needed. It could be related to the characteristics of the causative agent – pathogenicity and tropism for certain cells of the nervous system. Univariable logistic regression revealed that age and male sex are predictors for developing peripheral facial palsy. Findings of Rojko et al.¹⁴ showed that age and delayed diagnosis are factors associated with the unfavorable outcome of peripheral facial palsy based on multiple regression analyses.

It is very important for clinicians to know that patients with LNB may present symptoms and signs of encephalitis and myelitis. The rate of LNB encephalitis with or without myelitis was 13/103 cases (12.6%) in our study, similar to the German study¹¹ (12%), but higher than in the Danish study⁸ (3.7%). LNB presenting as encephalitis is scarcely reported in literature¹⁵. The most common sign of encephalitis in our study was cerebellar ataxia (9/13 cases, 69.2%). Three patients (3/103, 2.9%) presented delirium, one (1/103, 0.97%) presented stupor, and two (2/103, 1.9%) presented dysphasia. In the study by Knudtzen et al.¹⁵, ataxia was reported in 11/45 cases (24.4%), confusion/disorientation in 20/45 cases (44.4%), and aphasia in 3/45 cases (6.7%). In literature, such rare signs of LNB encephalitis as impaired vision¹⁶, dementia-like syndromes^{17,18}, and bilateral hearing loss¹⁹ are also reported.

We have found that patients with encephalitis and/or myelitis more often have a fever of $\geq 38^{\circ}\text{C}$, and pleocytosis of $\geq 300 \times 10^6/\text{l}$. This could be explained by a stronger inflammatory response in cases of encephalitis and/or myelitis compared to cases without the involvement of brain parenchyma. Astrocytes secrete inflammatory mediators following exposure to *B. burgdorferi* s.l. The studies also indicate that *Borrelia* can induce inflammatory responses in oligodendroglia and neuronal cells⁷. To find out more predictors and reasons for developing encephalitis and/or myelitis in patients with LNB, more studies are needed in endemic European countries. The results of our study showed that the rarest and most severe manifestation of early LNB is myelitis, which can result in death due to complications. Despite the rare occurrence, we, like other authors^{15,20}, suggest that every patient presenting aseptic encephalitis or myelitis has to be tested for *B. burgdorferi* s.l. in endemic areas because unfavorable outcomes are possible.

It is known that *B. burgdorferi* s.l. does not usually cause any inflammatory changes in blood, but can rather trigger pronounced inflammatory changes in CSF. In this study, like in other studies, no abnormalities were found in routine blood laboratory parameters of LNB patients,^{8,21} but all patients had abnormalities in CSF. During LNB, *B. burgdorferi* s.l. invades the CSF. The host immune system reacts to the spirochete with inflammation²². LNB is characterized by B-cell activation, plasma cell infiltration, and enhanced intrathecal antibody production⁷. It is important to emphasize that the absence of *B. burgdorferi* s.l. antibodies in serum does not exclude early LNB. Increased level of *B. burgdorferi* s.l. antibodies was found in CSF but not in serum in 17% of cases in the study of Henningsson et al.²¹, and in 4% of cases in our study.

In the present study, seven patients presented neuroimaging lesions. Most commonly reported cerebral MRI findings were non-enhancing T2 lesions which were present in 15 to 63% of patients²³ and were also present in more than a half of our patients' scans. However, the specificity of such lesions is disputed by Agarwal et al.²⁴, who did not observe the difference in incidence between LNB and control subjects. Confluent contrast-enhancing lesions that were present in one of our patients are also reported in individual cases by other authors^{24,25}. Other parenchymal manifestations of LNB include vasculitis²⁶, hemorrhage²³, mass lesions²⁷, or hemorrhagic encephalitis²⁸. Agarwal et al.²⁴ reported three cases of nerve enhancement that corresponded to clinical signs of cranial neuritis. This was also observed in four of our patients. As in our study, meningeal enhancement is rarely reported in patients with LNB meningitis^{1,24}. Lindland et al.²³ found eleven case reports of LNB myelitis with associated MRI lesions – the majority showed longitudinal extensive and centrally or anteriorly located lesions in cervical spinal cord. Schwenkenbecher et al.¹¹ reported MRI lesions located in cervical and thoracic segments in all five of their patients presenting with myelitis. We report two cases of spinal MRI lesions (transverse myelitis and segmental lesion of posterior column) located in upper thoracic segments. This might suggest that LNB myelitis does not have a strong predilection to a specific part of the spinal cord.

As much as 74% of LNB patients were discharged with unresolved symptoms or signs, the most common of which was unresolved peripheral facial palsy with a frequency of 39%. A total of 29% of patients had

residual symptoms at discharge in the study of Krogen et al.⁹. Our results showed that peripheral facial palsy was not the most common initial symptom, as it was reported in only 14% of cases. The onset of the disease more commonly manifested as radicular pain, reported in 71% of cases, while peripheral facial palsy and other neurological deficits usually manifested later. Based on our data, we conclude that timely diagnosis and treatment of LNB are important to reduce the frequency of unfavorable outcomes.

This report comes with its own limitations: the study was carried out retrospectively, it was impossible to perform a statistical analysis of late LNB due to the small number of patients, and not all patients were monitored for residual effects after discharge from the hospital.

Conclusion

The results of this retrospective study showed that polyradiculitis, reported in 75% of cases, was the most common neurological syndrome in patients with early LNB, and was also the most frequent first neurological sign but not the leading syndrome for hospitalization. Patients with polyradiculitis had delayed hospitalization. More than half of LNB patients developed peripheral facial palsy, and 14% of patients had encephalitis or myelitis. Absence of EM was the predictor of peripheral facial palsy, while female sex and untreated EM were predictors of isolated polyradiculitis. A fever of $\geq 38^{\circ}\text{C}$ and pleocytosis of $\geq 300 \times 10^6/\text{l}$ were associated with the development of encephalitis or myelitis in patients with early LNB.

Methods

Patients and study design

A retrospective study was performed to analyze the clinical and epidemiological features of LNB in hospitalized adults. The study took place in the Center of Infectious diseases and the Center of Neurology of Vilnius University Hospital Santaros Klinikos in 2010–2021. These are referral centers for adult infectious diseases and neurology in eastern Lithuania. They serve a population of 809 000, which is 27% of the country's population. Clinical and epidemiological data were collected from precisely documented medical records. The variables for the characterization of the cases were: age, sex, history of tick bite and EM, co-morbidities, dates (of tick bite, EM, onset of symptoms and signs, hospitalization, discharge), clinical presentation, laboratory tests, instrumental findings, treatment, symptoms and signs on discharge.

Definite LNB (DLNB) was diagnosed if patients fulfilled the following three criteria: 1) had neurological symptoms suggestive of LNB (with other causes excluded); 2) had pleocytosis of $\geq 10 \times 10^6/\text{l}$ in CSF; 3) had intrathecally produced *B. burgdorferi* s.l. antibodies. PLNB was diagnosed if two out of these three criteria were fulfilled²⁹. Early LNB was diagnosed if neurological symptoms and signs lasted for up to 6 months. Late LNB was diagnosed if neurological symptoms and signs presented for more than 6 months. Polyradiculitis was defined as the presentation of radicular pain with sensory impairment along

at least two nerve roots, with or without radicular paresis. Patients presenting only symptoms and signs of polyradiculitis, concomitant with CSF pleocytosis of $\geq 10 \times 10^6/l$, were classified as having isolated polyradiculitis. Patients presenting only peripheral facial palsy, concomitant with CSF pleocytosis of $\geq 10 \times 10^6/l$, were classified as having isolated peripheral facial palsy. Patients presenting symptoms and/or signs of brain damage such as focal neurological signs and/or impairment of consciousness, concomitant with CSF pleocytosis of $\geq 10 \times 10^6/l$, were diagnosed with encephalitis. Patients with bilateral motor, sensory, or autonomic dysfunction attributable to spinal cord, concomitant with CSF pleocytosis of $\geq 10 \times 10^6/l$, were diagnosed with myelitis. The diagnosis of EM was clinical: expanding red or bluish-red patch ($\geq 5\text{cm}$ in diameter), with or without center clearing³⁰.

2.2 Laboratory testing

Calculation of the Antibody Index (AI)

For the detection of intrathecal *B. burgdorferi s.l* antibodies production, CSF and peripheral blood samples were collected at the same time; IgG and IgM antibodies were analysed in one run at the Center of Laboratory medicine (Vilnius University Hospital Santaros Klinikos) using the quantitative immunoassay SERION ELISA classic *B. burgdorferi* IgG/IgM (Institut Virion/Serion GmbH, Wurzburg, Germany). Rheumatoid factors absorbent was used to pretreat samples before the IgM detection. To analyse dilution linearity of CSF and serum, the following combinations for dilutions of CSF and serum samples were used: CSF dilution 1:2 and 1:10, serum dilution 1:400 and 1:1000 (e.g., serum was diluted to CSF concentration). Concentrations of albumin, as well as total IgM and IgG levels in the CSF and serum were investigated by turbidimetric method using quantitative Optilite kits (The Binding Site Group Ltd., Birmingham, UK). In order to characterize the blood-CSF barrier functionality, as well as pathogen-specific antibodies production CSF/serum quotients of albumin, total and pathogen-specific IgM and IgG antibodies were calculated using SERION easy software, based on the scheme of prof. Hansotto Reiber. Borrelia-specific CSF/serum antibody index above 1.5 was considered to be pathological, indicative of intrathecal antibody synthesis directed against the pathogen, and supporting the diagnosis of LNB.

2.3 Statistical methods

Continuous variables are presented as median (interquartile range (IQR)). For categorical variables, absolute and relative frequencies were calculated. Mann-Whitney U test was used to compare continuous variables, and χ^2 test or Fisher's exact test was used to compare categorical variables. Univariable and multivariable binary logistic regression models were created to explore predictors associated with the development of isolated polyradiculitis, peripheral facial palsy, encephalitis and/or myelitis in patients with early LNB. Predictors were selected based on expert assessment. Odds ratio (OR) of 95% confidence interval (CI) was reported for logistic regression. P-value < 0.05 indicated statistical significance. IBM Statistical Package for the Social Sciences (SPSS) software version 20.0 was used for statistical analysis.

Declarations

Data availability

The datasets used and analyzed during this study are available from the corresponding author upon reasonable request.

Author contributions

D.R. wrote the main manuscript, organized this study, wrote the study protocol, collected and analyzed the data. J.U. performed the statistical analysis, revised the manuscript. A. J. analyzed the data, wrote the part about instrumental findings. A.K. analyzed the data, wrote the part about EMG, ENMG. R.M. analyzed laboratory data, wrote the paragraph *laboratory testing*. A.P. wrote the study protocol, analyzed the data. M.V. analyzed the data. G.K. revised the manuscript and supported with helpful discussions. All authors approved the final manuscript.

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Ethical statement

Vilnius Regional Biomedical Research Ethics Committee approved this study in 2022 (No. 2022/4-1426-897). The study was performed in accordance with the relevant guidelines and regulations. Informed consent was waived based on the Law on Biomedical Research of the Republic of Lithuania 2007, No. 125 - 5093 and the order of the director of the Lithuanian Bioethics Committee 2011, No. V – 28.

Competing Interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at

Correspondence and requests for materials should be addressed to D.R.

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Tables

Table 1. Baseline data and initial neurological symptoms and signs of patients with Lyme neuroborreliosis

Parameters	Value
Age, years, median (IQR); min-max, N = 103	60 (46-70); 18-90;
Sex, male, N (%)	50 (48.5)
History of tick bite \leq 120 days before LNB symptoms, N (%)	40 (38.8)
Pre-existing conditions, N (%)	56 (54.4)
Arterial hypertension	41 (39.8)
Diabetes	7 (6.8)
Incubation period (days), median (IQR); min-max, N = 27	35 (27-81); 10-113
Time from the onset of EM until the first symptom of LNB (days), median (IQR); min-max, N = 24	18 (14-36.3); 4-98
Time from the onset of LNB symptoms until hospitalization (days), median (IQR); min-max, N = 95	20 (8-31); 0-257
Defined LNB, N (%)	95 (92.2)
Possible LNB, N (%)	8 (7.8)
The presence of EM, N (%)	5/8 (62.5)
Isolated polyradiculitis	2
The presence of EM	2/2
Polyradiculitis + peripheral facial palsy	2
The presence of EM	1/2
Isolated peripheral facial palsy*	2
The presence of EM	0
Only lymphocytic meningitis	2
The presence of EM	2/2

The initial neurological symptoms and signs of early LNB, N (%)	
The radicular pain	
Peripheral facial palsy	71 (71)
Signs of encephalitis	14 (14)
Occipital neuralgia	10 (10)
	6 (6)

* concomitant with CSF pleocytosis, LNB Lyme neuroborreliosis, EM erythema migrans

Table 2. The predictors for developing isolated polyradiculitis, peripheral facial palsy and encephalitis or myelitis in patients with early LNB

	Univariable OR (95 % CI)	Multivariable OR (95 % CI)
Predictors for isolated polyradiculitis		
Age (years)	1.02 (1.00–1.05); p = 0.125	
Female sex	3.95 (1.59–9.80); p = 0.003	3.91 (1.45–10.55); p = 0.007
Untreated EM	3.26 (1.34–7.96); p = 0.009	3.24 (1.23–8.54); p = 0.018
Concomitant diseases	0.97 (0.42–2.25); p = 0.949	
Fever $\geq 38^{\circ}\text{C}$	0.20 (0.02–1.66), p = 0.137	
Pleocytosis $\geq 300 \times 10^6/\text{l}$	0.42 (0.13–1.37), p = 0.151	
Protein in CSF	0.50 (0.24–0.99), p = 0.045	0.65 (0.32–1.32); p = 0.230
Predictors for peripheral facial palsy		
Age (years)	0.98 (0.95–1.00); p = 0.049	0.98 (0.95–1.00); p = 0.088
Male sex	2.27 (1.02–5.07); p = 0.045	1.63 (0.66–3.97); p = 0.287
Absence of EM	2.49 (1.06–5.81); p = 0.036	2.84 (1.15–7.00); p = 0.024
Concomitant diseases	0.83 (0.38–1.83); p = 0.643	
Fever $\geq 38^{\circ}\text{C}$	0.56 (0.15–2.11); p = 0.390	
Pleocytosis $\geq 300 \times 10^6/\text{l}$	0.74 (0.28–1.94); p = 0.541	
Protein (g/l)	1.14 (0.74–1.78); p = 0.555	
Predictors for encephalitis or myelitis		
Age	1.01 (0.97–1.05); p = 0.676	
Male sex	2.67 (0.65–10.97); p = 0.174	
Untreated EM	0.95 (0.23–3.94); p = 0.943	
Concomitant diseases	1.23 (0.33–4.75); p = 0.738	
Fever $\geq 38^{\circ}\text{C}$	17.00 (3.67–78.74); p < 0.001	12.11 (1.88–77.78); p = 0.009
Pleocytosis $\geq 300 \times 10^6/\text{l}$	12.5 (2.88–54.25); p = 0.001	10.58 (1.67–67.03); p = 0.012
Protein (g/l)	2.09 (1.17–3.74); p = 0.013	1.00 (0.46–2.14); p = 0.989

EM – erythema migrans, CSF – cerebrospinal fluid

Variables with $p < 0.05$ in univariable regression were included into multiple regression models.

Model for isolated polyradiculitis: Hosmer and Lemenshow test $X^2 = 16.54$, $df = 8$, $p = 0.035$; Nagelkerke $R^2 = 0.245$.

Model for facial paresis: Hosmer and Lemenshow test $X^2 = 9.13$, $df = 8$, $p = 0.331$; Nagelkerke $R^2 = 0.142$.

Model for encephalitis or myelitis: Hosmer and Lemenshow test $X^2 = 6.64$, $df = 8$, $p = 0.576$; Nagelkerke $R^2 = 0.402$.

Table 3. Blood analysis of patients with Lyme neuroborreliosis

Variables	Early LNB	Late LNB
Leukocytes* $\times 10^9/l$, median (IQR), min-max, n	8.13 (6.35–9.7); 2.86–16; N = 99	55.9; 4.13–10.6; N = 3
CRP, mg/l, median (IQR), min-max, n	3.71 (1.31–5.84); 0.01–26.41; N = 94	2.5; 2–3; N = 3
ESR, mm/h median (IQR), min-max, n	9.5 (6–17); 1–88; N = 85	25; 7–25; N = 3
<i>B. burgdorferi</i> s.l. IgM positive, n (%)	79/100 (79)	2 (66.7)
<i>B. burgdorferi</i> s.l. IgG positive, n (%)	86/100 (86)	3 (100)
Both positive, n (%)	70/100 (70)	1 (33.3)
Both negative, n (%)	4/100 (4)	0

*The data of one patient with lymphocytic leukemia are excluded

Table 4. Cerebrospinal fluid analysis in patients with Lyme neuroborreliosis

Variables	Early LNB (all patients)	Cranial neuropathies*	Encephalitis*	Myelitis*	Late LNB
Pleocytosis, cellsx10 ⁶ /l, median (IQR); min-max; N	112 (57.75– 238.25); 12– 867	117 (69– 260.75); 19–867; N = 56	400 (93– 589); 45–613; N = 9	682.50 (592–0); 592–973; N = 2	230; 135– 305; N = 3
Lymphocytes %, median (IQR); min-max; N	97.5 (92– 100); (10– 100); N = 98	97 (90–100); 10–100; N = 55	98 (80.50– 100); 65–100; N = 5	51 (10– 92); N = 2	90; 21– 97; N = 3
Protein, g/l, median (IQR); min-max; N	1.10 (0.70– 1.65); 0.33– 6.09	1.23 (0.71– 1.69); 0.36– 6.09; N = 56	1.3 (0.84– 4.29); 0.70– 6.09; N = 9	3.41; 1.05–5.77; N = 2	3.3; 1.8– 6.47; N = 3
Glucose, mmol/l, median (IQR); min-max; N	3.04 (2.60– 3.44); 0.40–5.50	3 (2.58–3.50); 0.4–4.38; N = 55	2.9 (2.21– 3.73); 1.60– 5.50; N = 9	2.03; 0.4– 3.65; N = 2	2.6; 1.88– 3.1; N = 3
Intrathecal synthesis of <i>B. burgdorferi</i> s.l. IgM, N (%)	60/95 (63.2)	34/52 (65.4)	4/9 (44.4)	1/2 (50)	1/3 (33.3)
Intrathecal synthesis of <i>B. burgdorferi</i> s.l. IgG, N (%)	79/98 (77.6)	45/55 (81.8)	8/9 (88.9)	1/2 (50)	3/3 (100)

*Patients with early LNB.

LNB – Lyme neuroborreliosis, IQR – interquartile range

Normal values: protein (g/l) 0.15–0.45;

Figures

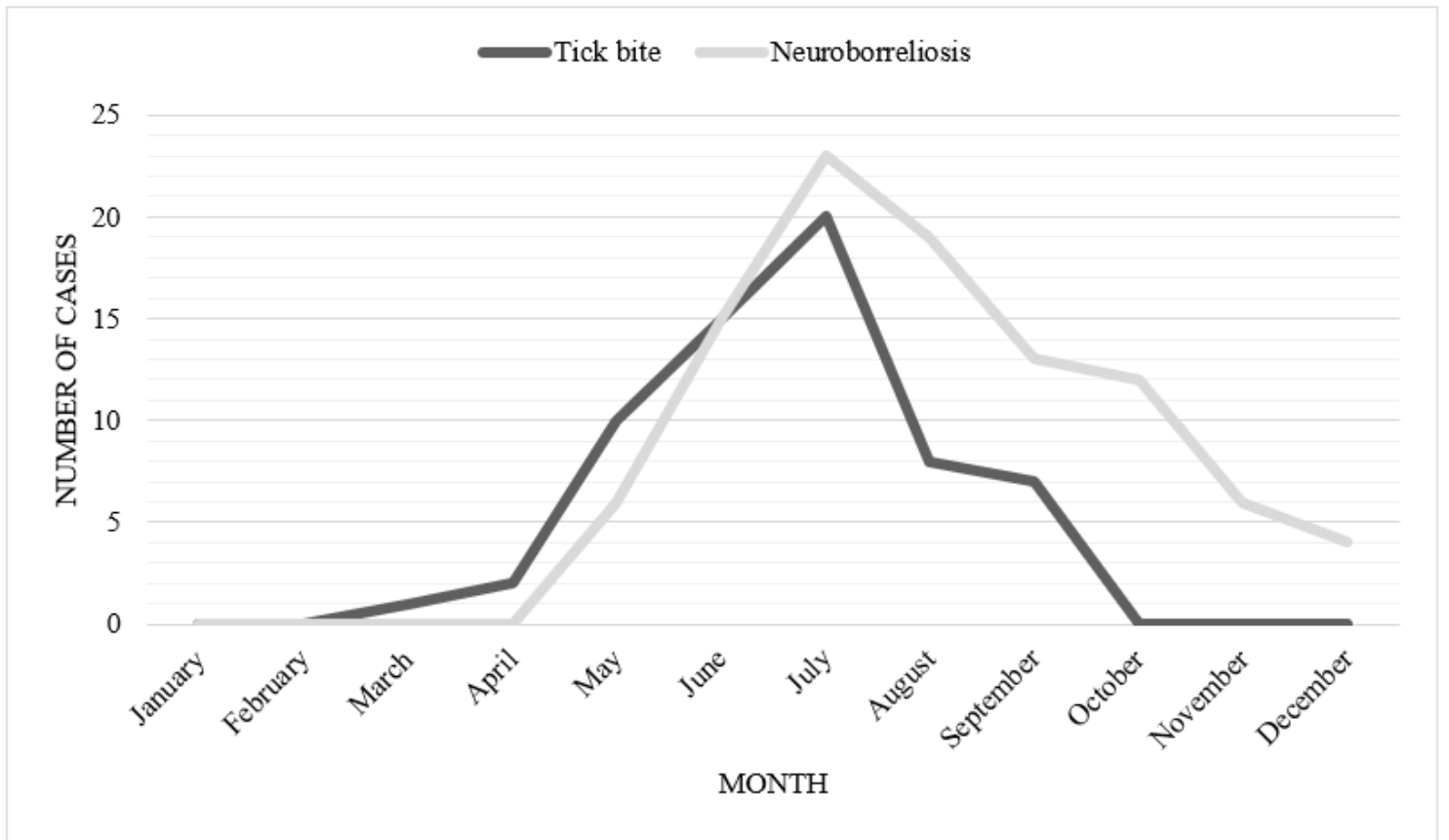


Figure 1

The seasonal distribution of reported tick bites and Lyme neuroborreliosis

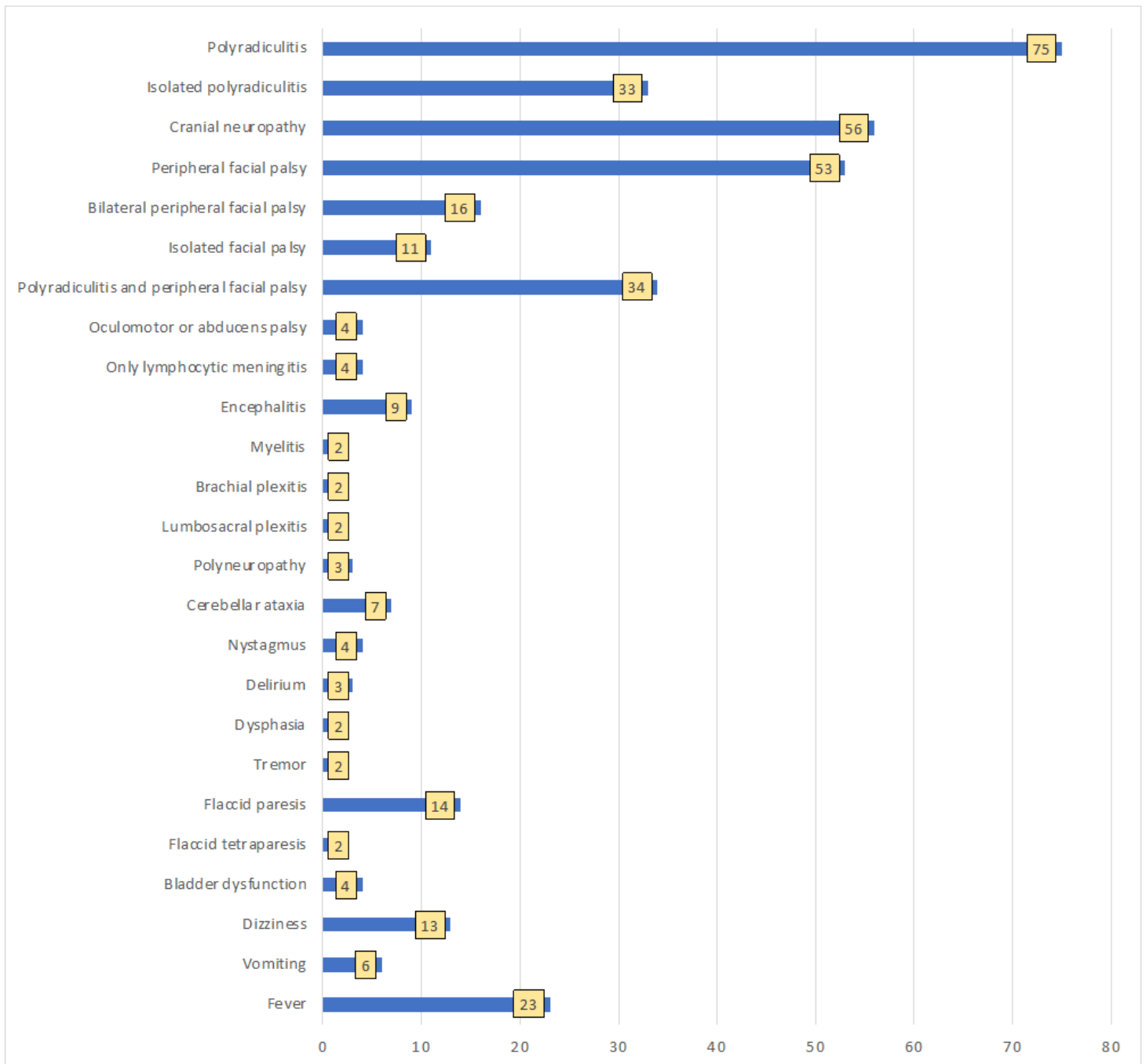


Figure 2

The clinical presentation of early Lyme neuroborreliosis, N = 100

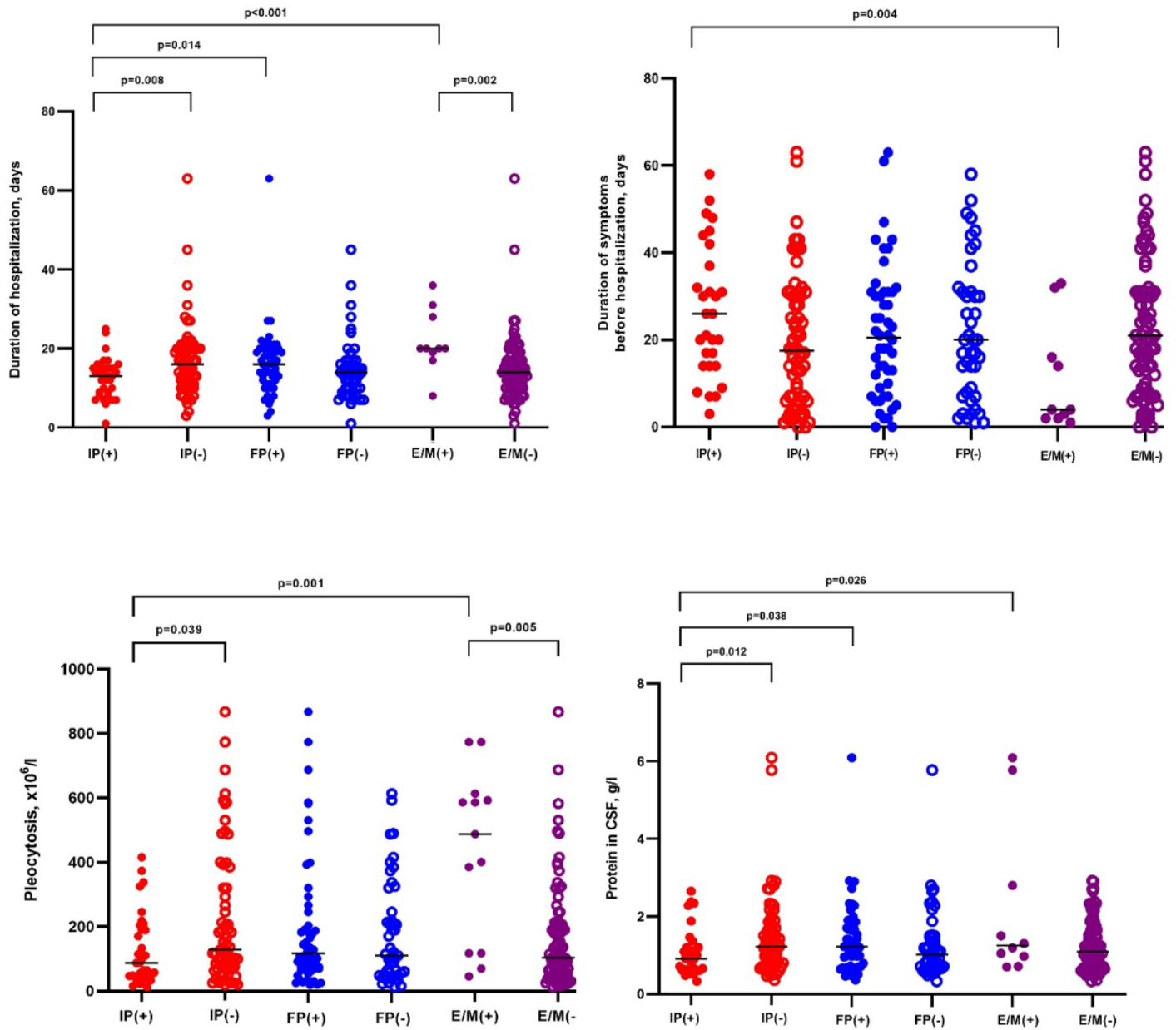


Figure 3

Comparison of duration of symptoms before hospitalization, duration of hospitalization, pleocytosis and protein in cerebrospinal fluid in patients with early Lyme neuroborreliosis

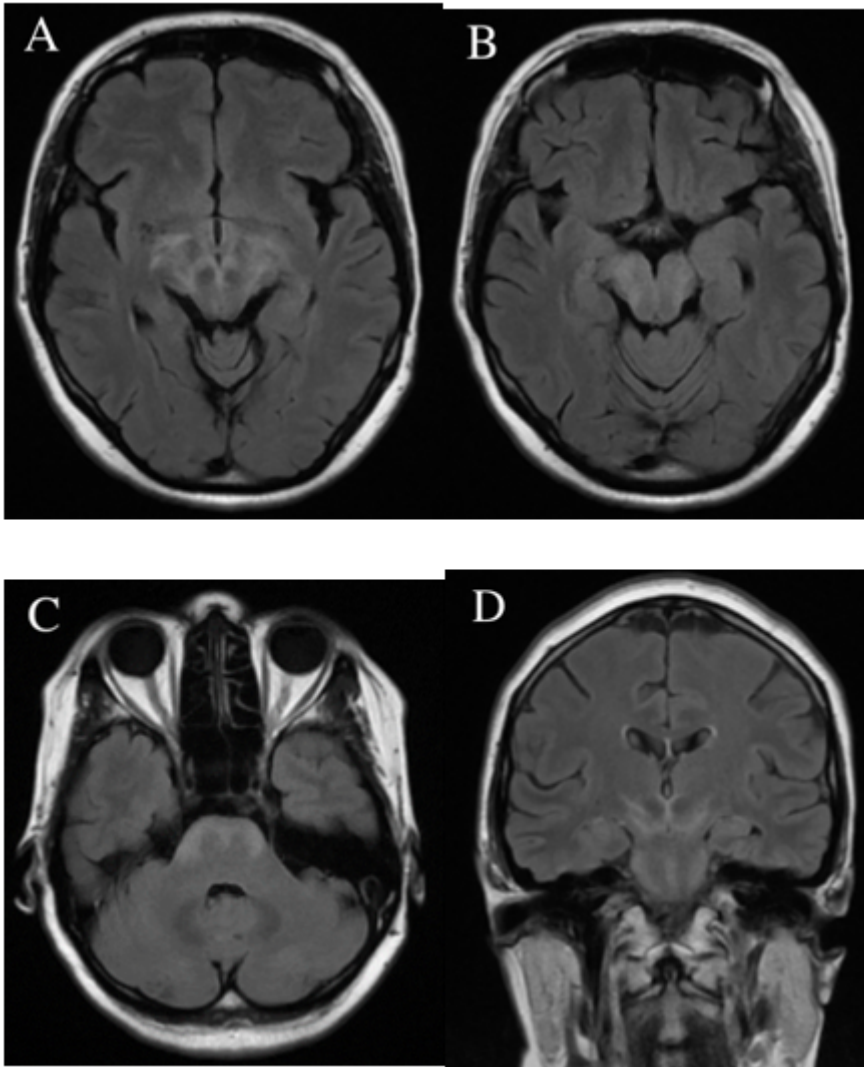


Figure 4

Head MRI of a patient diagnosed with Lyme neuroborreliosis (A-C – axial T2 FLAIR, D – coronal T2 FLAIR), showing confluent T2 hyperintense lesions involving basal ganglia, diencephalon, midbrain, and basal pons

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