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A retrospective study on differences in neuroborreliosis symptoms, signs and findings between adults and children

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Abstract

Objectives Lyme neuroborreliosis (LNB) presents with a broad range of symptoms and its incidence is increasing in Finland. This study examines clinical differences in LNB between adults and children (< 16 years), emphasizing head and neck symptoms, the prognostic value of laboratory tests, the findings in brain MRI, and the impact of glucocorticoids on facial palsy (FP) recovery.

Methods A retrospective analysis of LNB cases at Turku University Hospital (2011–2018) confirmed by intrathecal antibody production against *Borrelia* was conducted. With regard to cerebrospinal fluid pleocytosis, LNB was further classified as definite or possible. Patient characteristics were compared using appropriate statistical tests.

Results In total 159 adult and 25 child LNB patients were found. The most common symptom in adults was radiculitis (37% vs. 8%, $p=0.03$), while in children, it was FP (76% vs. 46%, $p=0.0052$). In children, the absence of FP was linked to delayed diagnosis (5.5 ± 9.1 weeks vs. 0.97 ± 0.92 weeks $p=0.043$). Of the pediatric LNB patients, 68% were seropositive for antibodies against *Borrelia* based on serum samples. Cranial nerve enhancement was observed in 26% of brain MRIs in the study cohort. No link between CSF findings or corticosteroid treatment and persisting FP was found.

Conclusions In adults, the most common manifestation related to LNB was radiculitis, whereas in children it was FP. One third of the pediatric patients were seronegative for antibodies against *Borrelia*, emphasizing the importance of CSF analysis in the diagnosis of LNB. Corticosteroids did not affect the recovery from FP and CSF findings had no prognostic value on recovery from FP.

Keywords Lyme neuroborreliosis, Facial palsy, Radiculitis, Sensorineural hearing loss, Cranial nerve enhancement, *Borrelia burgdorferi*

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Introduction

Lyme borreliosis (LB) is a tick-borne infection caused by *Borrelia burgdorferi* sensu lato (Bbsl; [1–3]. It is the most common vector-borne disease in Europe [4]. The incidence of LB varies between geographical regions, and in Finland it is highest in the south, particularly in the archipelago with an increasing area of occurrence [5]. The incidence of microbiologically confirmed disseminated LB cases was reported to be 31 per 100,000 population in 2014 [6]. After 2014, laboratory reports of LB positive serology have increased by 50%, and by 100% over the past 20 years [7].

From the tick bite site, the spirochete can spread by blood or along nerves to other parts of the body, including the central nervous system [8]. The central nervous system is affected in 3–12% of LB patients, expanding the infection to Lyme neuroborreliosis (LNB) [9]. In Europe and Asia, the two most common Bbsl species causing LNB are *Borrelia garinii* and *Borrelia afzelii* [10–12], whereas the only species in North America is *Borrelia burgdorferi* sensu stricto [9, 13].

The clinical presentation of LNB has been found to vary according to the causative Bbsl species [11]. The most common manifestations of LNB are radiculoneuritis, lymphocytic meningitis and cranial neurites, most commonly affecting the facial nerve causing facial palsy (FP) [5, 14, 15]. Also, other cranial nerves may be affected, causing a wide variety of symptoms [15–17]. Vestibulocochlear nerve involvement can result in a variety of ear-related symptoms [18], and the clinical presentation may be acute labyrinthitis with vertigo, sensorineural hearing loss, or tinnitus [19–25].

Around 40% of LNB patients suffer from FP [17, 26]. Fortunately, studies report that FP associated with LNB resolves completely in 57–86% of cases, and poor recovery from FP is associated with delays in the start of antimicrobial treatment [27, 28]. Also, the use of glucocorticoid therapy to treat FP is linked to poor recovery from the symptoms in some studies [29, 30], but not in all [28, 31, 32]. The possible negative effect of glucocorticoids on the resolution of LNB-related FP is a major concern, as they are the recommended treatment for Bell's palsy and should be initiated within a few days of symptom onset. *Borrelia* serology typically takes several days to complete and may be unreliable from both serum and CSF samples until at least six weeks have passed since the potential beginning of the infection [33]. At that point, the initiated treatment for Bell's palsy has usually already been completed. In endemic areas, LNB causes 20–65% of the FPs in pediatric population [34–38]. Fortunately, in pediatric patients persistent FP symptoms are infrequent, and in 8–13% of the patients some symptoms of FP remain [39, 40].

According to European Federation of Neurological Societies (EFNS) the diagnosis of LNB is considered definite, when all three of the following criteria are fulfilled: neurological symptoms suggestive of LNB without other obvious reasons, cerebrospinal fluid (CSF) pleocytosis and intrathecal *Borrelia* antibody production, and possible LNB, if only two of the criteria are met [33]. Based on the same guideline, when the clinical manifestation suggests LNB, it is recommended to investigate *Borrelia*-specific antibodies in both serum and CSF, as these results also form the basis for calculating intrathecal antibody production as well as signs of CSF inflammation as detected by pleocytosis. In addition, elevated CSF CXCL13, a B-cell–attracting chemokine, supports the diagnosis of acute LNB. Among patients with positive intrathecal antibody production, serum anti-*Borrelia* antibodies were negative in up to 20% of cases indicating that early diagnostics using only serum samples may increase the risk of false-negative results [17, 41].

Oral doxycycline is as effective as intravenous ceftriaxone in treating LNB in both adults and children [42–44]. However, over a month's delay in starting antibiotic treatment for LNB has been associated with the risk of residual symptoms and poorer perceived health-related quality of life [17, 45, 46].

Eight of the Bbsl species found in Europe are pathogenic to humans, but in Finland, *B. valaisiana*, *B. garinii*, and *B. afzelii* are mainly prevalent [12, 47]. Different Bbsl species favor different organs, which explains the differences in clinical manifestations between geographical areas [10, 48, 49], and even the organ preference of the same species has been found to vary depending on the genotype of the spirochete and the surface proteins it expresses [50–52]. For these reasons, regional studies are important. This retrospective study aims to characterize the clinical manifestation of LNB in children and adults, evaluate the predictive value of laboratory diagnostics, and the effect of glucocorticoid treatment of LNB-related FP. The study was conducted at Turku University Hospital, Finland, a tertiary care center serving a region endemic to Lyme borreliosis, and included patients treated between 2011 and 2018.

Materials and methods

Study design and ethics

This was a retrospective cohort study approved by the institutional review committee of the Hospital District of Southwest Finland (Ref: T06/029/18). As this was a retrospective study, the ethical committee or informed consent was not required under the Finnish national legislation.

Subjects

The study subjects were patients treated for LNB in the tertiary referral center in the hospital district of Southwest Finland (475 000 inhabitants), Turku University Hospital, between the first of January 2011 and 31st of December 2018. A database search from the Turku University Hospital laboratory database was conducted. For inclusion in the study, the patient had to have intrathecal *Borrelia*-specific antibody production, classified as positive (>0.3) IgM and/or IgG antibody index, symptoms suggesting LNB, and received antimicrobial treatment for LNB. The disease was classified as definite LNB if CSF pleocytosis (>5 leukocytes/μL) was also present. If this third criterion was not met, the case was classified as possible LNB. The medical records and laboratory database of these patients were retrospectively reviewed, and corticosteroid therapy was administered based on clinical judgment without predefined selection criteria.

Statistics

The categorical variables are presented in numbers and percentages, and the differences between the study groups were analyzed using Pearson's chi-squared test. The normal distribution of the continuous variables was inspected utilizing histogram plots and tested with the Kolmogorov–Smirnov test. As most of the continuous laboratory test values and duration between onset of symptoms and diagnosis of LNB were not normally distributed, the differences between groups were analyzed using Mann-Whitney U test. In contrast, the delay between seeking treatment in patients who did and did not recover from FP within 52 weeks was normally distributed and therefore analyzed using a t-test. The level of statistical significance was determined to be p-values less than 0.05. All statistical analyses were conducted using SPSS 29 (IBM, Armonk, NY, USA). Since leukocytes in the blood can interfere with the estimation of leukocytes in the CSF, one leukocyte per 1,000 erythrocytes in the CSF was approximated to originate from blood.

Results

Patient demographics

In total, 184 patients were found, of which 159 were adults and 25 children (<16 years of age). Two adult patients were diagnosed with LNB twice during the study period, and in the following analyses, these second episodes of LNB were handled as a new individual had got LNB for the first time. For one patient, the first episode met the criteria for definite LNB, while the second episode was classified as possible LNB; however, the clinical presentation was consistent with LNB, and antibiotic treatment was initiated. For the other patient, both episodes fulfilled the criteria for definite LNB, and during the second episode, CSF CXCL13 was elevated, indicating a new episode of neuroborreliosis. Neither patient had a known immunodeficiency nor were they on immunosuppressive medication. Also, three additional patients had an earlier episode of LNB at least a decade before the second LNB evaluated in this study. For fourteen patients, the diagnosis of LNB was not definite, as they did not have pleocytosis in the CSF. Because of the symptoms eligible for LNB, antibiotic treatment, and intrathecal antibody production, these patients were also included in the study. Some patients received two courses of antibiotics, either due to an insufficient response to the initial treatment or for practical reasons, such as switching from intravenous ceftriaxone to oral doxycycline. As randomized trials have shown oral doxycycline to be as effective as intravenous ceftriaxone in treating LNB, no comparisons between antibiotic regimens were made in this study. The patient demographics in detail can be found in Table 1.

Symptoms and signs, and imaging

A wide range of symptoms are related to LNB. The general, truncal and limb-related symptoms and signs are shown in Table 2, and detailed symptoms in the head and neck area are presented in Table 3. Adult patients suffered more often than children from radiculitis (37% vs. 8%, $p=0.03$), pain (49% vs. 4%, $p<0.001$), paresthesia (40% vs. 4%, $p=0.019$), and decreased general condition (27% vs. 8%, $p=0.042$). In contrast, children had more often LNB-related FP than adults (76% vs. 46%, $p=0.0052$). Also, children had more often facial swelling on the same side as the FP (12% vs. 0%, $p<0.001$) and suffered from ear pain more often than adults (12% vs. 2%, $p=0.02$).

No significant differences were detected in the duration between the onset of symptoms and initiation of antimicrobial treatment between patients who did and did not recover from FP within 52 weeks (4.4 ± 4.6 and 3.3 ± 2.3 weeks, mean ± SD, $p=0.30$). Also, as shown in Table 4, no differences were detected in the persisting FP frequencies between the adult patients treated with and without corticosteroid in the 1, 3, 6, and 12-month follow-up visits.

For all patients, the time from symptom onset to LNB diagnosis was significantly shorter in those with FP compared to patients without facial nerve involvement (4.3 ± 4.4 weeks vs. 6.4 ± 5.6 weeks, $p<0.001$). For pediatric patients this is especially pronounced, as when FP was one of the symptoms, the mean delay between onset of symptoms and LNB diagnosis was 0.97 ± 0.92 weeks while this delay in patients without FP was 5.5 ± 9.1 weeks ($p=0.043$). For adults, no differences in the delay between patients with and without FP were detected. Table 5 presents the persisting symptoms and signs observed twelve months after treatment for LNB.

Table 1 Patient demographics, characteristics of EM, and antibiotic treatment of LNB

Characteristic	Adults	Children	Total
Number of patients	161 (86%)	25 (13%)	186 (100%)
Female sex, no. (%)	68 (42%)	10 (40%)	78 (42%)
Age, mean (SD; range)	58.3 (16.8; 17-87)	8.4 (3.9; 3.1-15.4)	51.6 (23.2; 3.1-87)
Definite LNB	148 (92%)	24 (96%)	172 (92%)
Possible LNB*	13 (12%)	1 (4%)	14 (8%)
Activity exposing for a tick-bite**	48 (30%)	1 (4%)	49 (26%)
Previous tick-bite			
One	52 (32%)	11 (44%)	63 (34%)
Several	33 (20%)	2 (8%)	35 (19%)
Previous erythema migrans during the last year	37 (23%)	5 (20%)	42 (23%)
Solitary	32 (86%)	4 (80%)	36 (86%)
Multiple	5 (14%)	1 (20%)	6 (14%)
Location of erythema migrans			
Head and neck	1 (3%)	5 (100%)	6 (14%)
Torso and extremities	33 (87%)	0 (0%)	33 (77%)
Unknown	3 (8%)	0 (0%)	4 (9%)
Received treatment for the EM	7 (19%)	1 (20%)	8 (19%)
Duration of the symptoms before the start of treatment in weeks (SD; range)	5.8 (5.0; 0-28)	2.1 (4.7; 0-24)	5.3 (5.1; 0-28)
Relief of the symptoms before the start of treatment	19 (12%)	0 (0%)	19 (10%)
Received oral glucocorticoids before the start of treatment	43 (27%)	4 (16%)	47 (25%)
Antibiotic treatment for LNB			
Ceftriaxone	107 (66%)	2 (8%)	109 (59%)
Doxycycline	52 (32%)	22 (88%)	74 (40%)
Amoxicillin	1 (1%)	0 (0%)	1 (1%)
Cefuroxime	0 (0%)	1 (4%)	1 (1%)
Piperacillin-tazobactam	1 (1%)	0 (0%)	1 (1%)
Second antibiotic treatment for LNB			
None	115 (71%)	20 (80%)	136 (73%)
Ceftriaxone	9 (6%)	2 (8%)	11 (6%)
Doxycycline	32 (20%)	3 (12%)	35 (19%)
Ceftriaxone + doxycycline	1 (1%)	0 (0%)	1 (1%)
Ampicillin	1 (1%)	0 (0%)	1 (1%)
Ampicillin + vancomycin	1 (1%)	0 (0%)	1 (1%)
Cephalexin + metronidazole	1 (1%)	0 (0%)	1 (1%)
*positive intrathecal anti-Borrelia antibodies and symptoms suggesting LNB without CSF pleocytosis.			
**Outdoor recreation or hobbies, gardening, agricultural work and exposure to outdoor pets or other animals.			

The brain of 68 out of 161 adult and 4 out of 25 pediatric patients (42% vs. 16%, $p = 0.012$) were imaged with MRI. These findings are presented in Table 6. Patients who underwent MRI were selected based on the clinicians' judgment without predefined criteria. Out of 72 patients who had a brain MRI, 53 (74%) did not show enhancement of cranial nerves. Enhancement of a single nerve was found in 13 (18%) patients and multiple nerve enhancement in 6 (8%) patients. One patient had a radiologically diagnosed optic neuritis with decreased visual acuity and papilloedema, as well as oculomotor and vestibulococlear neuritis with vertigo and hearing loss. The diagnosis of LNB was classified as definite and hearing loss, vertigo and reduced visual acuity improved after LNB treatment. Only one out of five patients with neuritis of the oculomotor nerve had diplopia, while both patients with neuritis of the abducens nerve in MRI had diplopia and clinical abducens paresis. The second patient with abducens neuritis also had oculomotor neuritis without any clinical findings or diplopia. None with oculomotor neuritis had ptosis, and none with trigeminal neuritis had facial pain. All 14 patients with facial neuritis also had FP. In one of these patients, the FP was not resolved within 52 weeks and was considered permanent. Two patients had glossopharyngeal, one vagal and one accessorial neuritis, and no symptoms related to these conditions. The patient with hypoglossal neuritis also had a deviation of the tongue. One patient with vestibulocochlear neuritis had hearing loss but no vertigo and the recovery from hearing loss was only partial.

Table 2 The general, truncal and limb-related symptoms and signs related to LNB

Symptom	Adults (n=161)	Children (n=25)	Total (n=186)	*p* -value
Headache	80 (50%)	14 (56%)	94 (50%)	0.56
Neck pain	69 (43%)	7 (28%)	76 (41%)	0.16
Radiculitis	**61 (37%)**	**2 (8%)**	**63 (34%)**	**0.003**
Radicular Pain	**103 (64%)**	**8 (32%)**	**111 (60%)**	**0.002**
Torso	21 (13%)	3 (12%)	24 (12%)	
Upper extremities	6 (4%)	1 (4%)	7 (4%)	
Lower extremities	5 (3%)	1 (4%)	6 (3%)	
Paresthesia	**79 (49%)**	**1 (4%)**	**80 (43%)**	
Torso	16 (10%)	0 (0%)	16 (9%)	
Upper extremities	17 (11%)	0 (0%)	17 (9%)	
Lower extremities	13 (8%)	0 (0%)	13 (7%)	
Muscle weakness/Paresis	**40 (25%)**	**1 (4%)**	**41 (22%)**	
Upper extremities	6 (4%)	0 (0%)	6 (3%)	
Lower extremities	20 (12%)	1 (4%)	21 (11%)	
All extremities	10 (6%)	0 (0%)	10 (5%)	
Stiffness of the neck	19 (12%)	4 (16.0%)	23 (12%)	0.55
Monoarthritis	2 (1%)	0 (0%)	2 (1%)	0.58
Polyarthritis	2 (1%)	0 (0%)	2 (1%)	0.58
Arthralgia	49 (30%)	3 (12%)	52 (28%)	0.056
Bannwarth syndrome	31 (19%)	2 (8%)	33 (18%)	0.17
Fatigue	68 (42%)	11 (44%)	79 (42%)	0.87
Fever	42 (26%)	8 (32%)	50 (27%)	0.54
Decrease in the general condition	43 (27%)	2 (8%)	45 (24%)	**0.042**
Nausea	33 (20%)	6 (24%)	39 (21%)	0.69
Weight-loss	18 (11%)	9 (36%)	18 (10%)	0.08
Cognitive problems				
Subjective memory difficulties	15 (9%)	0 (0%)	15 (8%)	0.11
Memory difficulties confirmed by a healthcare professional	11 (7%)	0 (0%)	11 (6%)	0.18
Other cognitive impairments*	21 (13%)	1 (4%)	22 (12%)	
Tremor	13 (8%)	1 (4%)	14 (8%)	
Lymphocytoma	2 (1%)	0 (0%)	2 (1%)	0.58
*confusion, delirium or executive function disturbances				

Laboratory tests

The *Borrelia* serology was investigated in 179 patients, and the IgG antibodies tested positive for 154 (86%) patients, and the seven untested patients were adults. Positive *Borrelia* serologies were found in 137 (89%) adults and 17 (68%) children. No significant differences in initial CSF findings were observed between patients who did and did not recover from FP within 12 months (Table 7).

Hearing loss

In this cohort, nine adults and two children had hearing loss as a symptom. Audiograms were examined in five of these adults. Two had bilateral sensorineural hearing loss, predominantly affecting high frequencies (possible age-related hearing loss). Two others had unilateral moderate sensorineural hearing loss, and the fifth had unilateral severe sensorineural hearing loss. In the two adults with unilateral moderate sensorineural hearing loss, it was partially resolved in both at follow-up audiograms. The fifth, who had severe sensorineural hearing loss, had no follow-up.

In children, one had bilateral mild sensorineural hearing loss, which completely resolved in the follow-up audiogram on one side and partially on the other. The other child had bilateral severe sensorineural hearing loss, which was partially resolved in one ear but not at all in the other ear during the follow-up.

Discussion

In this study, the clinical manifestations of LNB between adults and children were compared. The most common symptoms of LNB in adults were radicular pain, paresthesia, and muscle weakness, while children suffered

Table 3 Head and neck symptoms and signs related to LNB

Symptom	Adults (n=161)	Children (n=25)	Total (n=186)	*p* -value
Facial nerve palsy	**74 (46%)**	**19 (76%)**	**93 (50%)**	**0.0052**
Bilateral	13 (8%)	0 (0%)	13 (7%)	
Swelling of face related to FP	0 (0%)	3 (12%)	3 (2%)	**<0.001**
Hypogeusia	14 (9%)	1 (4%)	15 (8%)	
Vocal cord palsy	2 (1%)	0 (0%)	2 (1%)	0.58
Hoarseness	6 (4%)	0 (0%)	6 (3%)	0.325
Abducens nerve palsy	5 (3%)	0 (0%)	5 (3%)	0.37
Ptosis	2 (1%)	0 (0%)	2 (1%)	0.58
Diplopia	14 (9%)	0 (0%)	14 (8%)	0.125
Other visual problems than diplopia	21 (13%)	1 (4%)	22 (12%)	
Tinnitus	12 (7%)	1 (4%)	13 (7%)	0.53
Hearing loss	9 (6%)	2 (8%)	11 (6%)	0.64
Hypersensitivity to sounds	1 (1%)	1 (4%)	2 (1%)	0.13
Vertigo	51 (32%)	5 (20%)	56 (30%)	0.24
Sense of pressure in the ear	2 (1%)	0 (0%)	2 (1%)	0.58
Ear pain	4 (2%)	3 (12%)	7 (4%)	**0.02**
Pain behind the ear	3 (2%)	0 (0%)	3 (2%)	0.49
Facial pain	2 (1%)	1 (4%)	3 (2%)	
Paresthesia of the head and neck	15 (9%)	1 (4%)	16 (9%)	
Neck	2 (1%)	0 (0%)	2 (1%)	
Face	3 (2%)	0 (0%)	3 (2%)	
Top of the head	7 (4%)	0 (0%)	7 (4%)	
Several or all	3 (2%)	1 (4%)	4 (2%)	
Deviation of the tongue	1 (1%)	1 (4%)	3 (2%)	
Throat pain	0 (0%)	1 (4%)	1 (1%)	
Pain in the tongue	0 (0%)	1 (4%)	1 (1%)	
Paresthesia of the tongue and mouth	2 (1%)	0 (0%)	2 (1%)	0.58
Palsy of the palatine	1 (1%)	0 (0%)	1 (1%)	
No pharyngeal reflex	2 (1%)	0 (0%)	2 (1%)	0.58

Table 4 The frequency of persisting facial nerve palsy in adult patients treated with and without oral glucocorticoids initially and at 1-, 3-,6-, and 12-month follow-up appointments

	Patients treated with glucocorticoids	No glucocorticoids	*p* -value
Initially	41	33	
1 month	33	23	0.282
3 months	21	12	0.201
6 months	11	5	0.255
12 months	4	3	0.923

Table 5 Persisting symptoms and signs twelve months after the treatment of LNB*

No follow-up	112 (60%)
No symptoms	36 (19%)
Headache	2 (1%)
Stifness of the neck	3 (2%)
Arthalgia	3 (2%)
Muscle pain	3 (2%)
Radiculitis	11 (6%)
Paresthesia	13 (7%)
Tinnitus	1 (1%)
Hearing loss	1 (1%)
Vertigo	3 (2%)
Fatigue	7 (4%)
Diagnosed cognitive impairment	5 (3%)
Decreased general condition	1 (1%)
Other visual problems than diplopia	2 (1%)
Facial nerve palsy	7 (4%)
Other peripheral nerve palsies	2 (1%)
*Follow-up data was available for 74 patients, out of all those included in the study (both children and adults).	

Table 6 The cranial nerve enhancement findings on magnetic resonance imaging of the brain in LNB patients

Finding	Adults (n=161)	Children (n=25)	Total (n=186)
Magnetic resonance imaging (MRI) of the brain	**68 (42.2%)**	**4 (16%)**	**72 (38.7%)**
Olfactory nerve	0 (0%)	0 (0%)	0 (0%)
Optic nerve	1 (1%)	0 (0%)	1 (1%)
Oculomotor nerve	5 (7%)	0 (0%)	5 (7%)
Trochlear nerve	0 (0%)	0 (0%)	0 (0%)
Trigeminal nerve	3 (4%)	1 (25%)	4 (6%)
Abducens nerve	2 (3%)	0 (0%)	2 (3%)
Facial nerve	12 (18%)	2 (50%)	14 (19%)
Vestibulocochlear nerve	1 (1%)	1 (25%)	2 (3%)
Glossopharyngeal nerve	2 (3%)	0 (0%)	2 (3%)
Vagus nerve	1 (1%)	0 (0%)	1 (1%)
Accessorial nerve	1 (1%)	0 (0%)	1 (1%)
Hypoglossal nerve	1 (1%)	0 (0%)	1 (1%)
Other neuritis	3 (4%)	0 (0%)	3 (4%)
Percentages refer to patients imaged with MRI.			

Table 7 Comparison of CSF findings in FP ($n=93$) patients who did and did not recover within 12 months

CSF finding median (IQR)	Persistent FP ($n=7$)	Recovered from FP within 12 months ($n=67$)	*p*-value
Leukocytes (/µL)	260 (42–600)	116 (63–255)	0.15
Protein (mg/L)	1671 (747–1840)	1143 (697–1730)	0.54
Lactate (mmol/L)	2.8 (2.2–3.45)	2.25 (1.90–2.68)	0.11
CXCL13 (pg/mL)	3155 (820–4422)	1035 (276-10500)	0.98

from FP and pain in ear region more often than adults. This is in line with earlier studies, which reported that adults suffer more often from muscle weakness, muscle pain, and paresthesia than children [17, 53, 54]. The incidence of LNB-related facial palsy in adults versus children remains controversial: a Dutch study, like ours, found higher rates in children [54], whereas a Polish study reported the opposite [53]. Since children experience facial paralysis more frequently than adults, it is unsurprising that they also report ear pain more often. This can be explained by the sensory innervation of the external ear, which is supplied by the facial nerve along with the trigeminal, glossopharyngeal, vagus, and

cervical nerves. Also, earlier studies reported that LNB causes headaches more often in children than in adults [17, 54] and more vertigo in adults than in children [53]. While in our cohort, both headache and vertigo were frequent findings, and occurred with similar frequency across both patient groups. In our study, three children with FP exhibited ipsilateral facial swelling, a symptom recognized decades ago as a possible EM change that helped to differentiate LB-related FP from Bell's palsy [55]. This symptom is rare in adults (3%) and absent in our adult patients [28].

In pediatric population, the presence of FP leads to LNB diagnosis markedly faster when compared to situations where LNB is manifested with other symptoms. It is easy for parents to detect abnormalities in facial function, whereas it might be difficult for a child to communicate mild vertigo, hearing loss or pain to the parents and/or legal guardians. However, adult patients seem to be diagnosed with LNB at a similar delay regardless of whether FP is present or not. However, some symptoms are difficult to identify to be caused by LNB. Even though radicular pain is a typical symptom of LNB, it has been associated with a longer treatment delay [17]. The duration between the onset of symptoms and initiation of antimicrobial treatment did not differ between patients who did and did not recover from FP.

The second goal of our study was to assess the effect of corticosteroid treatment on recovery from LNB-related FP. The outcome from FP in our pediatric patients was extremely favorable, and regardless of whether they received corticosteroid treatment or not and differences in antibiotic treatments, no one was left with a verified permanent FP. Previously, both in Finland and Sweden, approximately one-fifth of children have been found to have residual symptoms of FP associated with LNB [39, 56].

The use of corticosteroid treatment and its possible harms has remained controversial in the treatment of LNB-related FP. Although some studies have raised concerns that corticosteroids combined with antimicrobial therapy may increase the risk of permanent facial nerve dysfunction in LNB [29, 30], others have suggested that corticosteroid treatment does not interfere with the FP recovery [28, 31]. In our cohort, only seven adult patients (9%) did not fully recover and were left with permanent FP, and no differences in corticosteroid use were detected between patients that did and did not recover completely from the FP. Also, as there were no differences in patient numbers between the groups at follow-up, it is likely that receiving corticosteroid treatment does not delay recovery or increase the risk of persisting FP. Consistent with our findings, previous studies from the United States have also reported that corticosteroids do not affect the course or final recovery of LNB-related FP [32]. These findings further suggest that corticosteroid treatment does not delay the recovery from LNB-associated FP and does not increase the risk of residual paresis in the European LNB. The evaluation of glucocorticoid treatment effects in this retrospective study is inherently limited by potential selection bias, as treatment allocation was not randomized. In our cohort, patients receiving corticosteroids were treated based on clinicians' discretion rather than predefined criteria. To more reliably assess the efficacy of glucocorticoid therapy for LNB-related facial palsy, prospective randomized controlled trials would be necessary.

Nine out of ten adult LNB patients were seropositive for antibodies against *Borrelia*. In contrast, a markedly lower proportion of pediatric patients were seropositive, which was even lower than previously reported [34]. Considering this, up to one-third of LNBs could be misdiagnosed if relying solely on serological findings when CSF analysis is not performed, highlighting the importance of this investigation in the pediatric population. It is possible that children frequently seek medical care early in the course of infection and at this timepoint have not yet turned positive in serology. It could be speculated that if *Borrelia* spirochetes have crossed the blood brain barrier early, intrathecal antibody production may reach the sensitivity level of positivity even faster than that of antibodies in serum. Additionally, no differences in CSF findings were observed between adult patients who recovered from FP within 12 months and those who did not.

Inflammation related to LNB may cause meningeal or cranial nerve enhancement on MRI. While a 2009 study reported such enhancement in only 5% of LNB patients [57], more recent studies found facial nerve enhancement in 17% of LNB-related facial palsy cases [58], and a Norwegian cohort showed enhancement in one cranial nerve in up to 57% and multiple nerves in 19% of LNB patients [59]. We observed clinical FP in a higher proportion of patients than neuritis detected by MRI. Compared to the 57% found in the Norwegian study, in our cohort, only 26% of our patients showed cranial nerve enhancement on MRI.

The enhancement of the facial nerve is associated with FP [59], and although it was not observed in all FP patients in our cohort, all patients with facial nerve enhancement had clinical FP. In contrast to the Norwegian study, both of our patients with vestibulocochlear nerve enhancement suffered from either vertigo or hearing loss. As previously reported and observed in our cohort, other cranial nerves in addition to the facial nerve, may show enhancement on MRI images but this rarely manifests as clinical symptoms [59]. A previous study reported cochlear enhancement in LNB-related hearing loss, but in our study some patients had hearing loss without MRI findings, likely due to limited sensitivity of conventional MRI [60]. Conventional MRI is not currently

central to LNB diagnosis but serves primarily in differential diagnosis. However, advances in imaging techniques may enable new applications in the future. Vertigo is an interesting symptom, as it was common in both age groups despite relatively infrequent imaging abnormalities of the vestibulocochlear nerve (3%). This suggests that vertigo in LNB may arise from multiple mechanisms in addition to vestibulocochlear nerve involvement.

Acute hearing loss has been associated with LB in serological studies [19, 20, 23–25]. Similar to our findings, earlier studies from Finland and Norway reported that 1–5% of adult LNB patients experienced hearing loss as a subjective symptom [43, 61]. Both reversible and prolonged cochlear dysfunction, assessed via pure-tone audiogram and otoacoustic emissions, are associated with LNB in up to two-thirds of adult patients [62]. Otherwise, published data on LNB-related hearing loss is mainly limited to case reports [63, 64]. It seems that despite recent studies, the contribution of LNB to vestibulocochlear nerve symptoms is still poorly understood and might be under-reported, thus needing more attention. Our study demonstrates that LNB can cause transient and permanent dysfunction not only in the facial nerve but also in the vestibulocochlear nerve and be a rare but considerable cause of sensorineural hearing loss.

Conclusion

In our retrospective study, the most common symptoms and signs related to LNB were radiculitis, pain, paresthesia and muscle weakness in adults and FP and in the pediatric population. Although not a common symptom overall, ear pain was more frequently observed in children than in adults. Children may struggle to articulate LNB-related symptoms other than FP, potentially delaying diagnosis of LNB when FP is absent. Corticosteroid treatment does not seem to delay the recovery from LNB-related FP or increase risk of permanent FP. No differences were detected in CSF analysis of LNB patients that did and did not recover completely from FP within one year. Only two thirds of pediatric LNB patients confirmed with intrathecal antibody production against *Borrelia* had a positive *Borrelia* serology. Our results emphasize the importance of CSF analysis in the diagnostic strategy regarding suspicion of LNB since several LNB patients did not show seropositivity at the time of diagnosis. MRI is not central to the diagnosis of LNB but may provide additional information and assist in differential diagnosis. LNB should be recognized as a potential cause of both transient and permanent sensorineural hearing loss.

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Author contributions
All authors participated in various stages of the research, and read and approved the final manuscript.

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Data availability
The datasets generated during the current study is not publicly available due to patient confidentiality but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This was a retrospective cohort study approved by the institutional review committee of the Hospital District of Southwest Finland. As this was a retrospective study, the ethical committee or informed consent was not required under the Finnish national legislation.

Competing interests
The authors declare no competing interests.

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