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Plasma neurofilament light significantly decreases following treatment in Lyme neuroborreliosis and not associated with persistent symptoms

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Total word count: 3399

Short running title: NfL LNB

Keywords: Lyme neuroborreliosis, biomarker, Neurofilament Light chain, neuroinflammation, persistent symptoms

Abstract

Background: Currently there is an unmet need for a highly standardized blood biomarker test to monitor treatment response in Lyme neuroborreliosis (LNB). Differentiating between active or past infection is challenged by the relatively high frequency of persistent symptoms after the end of antibiotic treatment (estimated 15-20%), variable clinical course and the long-lasting *B. burgdorferi* antibodies. We therefore wanted to evaluate plasma NfL as a marker for disease activity in LNB.

Methods: Prospective included cohort of definite LNB (N=36) with blood samples and clinical evaluation including Glasgow Outcome Score (GOS) at treatment initiation, 3- and 6-months follow-up. Consecutive plasma was retrospectively analyzed for the content of NfL by Quanterix® kits (Simoa® NF-light Kit).

Results: pNfL significantly decreased between treatment initiation and 3-months follow-up (median 83 pg/ml vs median 14 pg/ml (25 pairs), p<0.0001). No significant change was observed between 3- and 6-months follow-up (median 14 pg/ml vs median 12 pg/ml (21 pairs), p=0.33). At treatment initiation 90% had pNfL above the age defined reference compared to only 23% and 7% respectively at 3- and 6-months follow-up. Decreases in pNfL were mirrored by increasing GOS. Reporting persistent symptoms at the 6 months follow-up was not associated with plasma NfL (relative change from reference or actual values) at baseline or at 6 months follow-up

Conclusion: pNfL decreases following antibiotic treatment in LNB and is not associated with reporting persistent symptoms. We therefore speculate that it may prove useful as a treatment response biomarker in LNB.

Introduction

Background

Lyme neuroborreliosis (LNB) caused by infection with the spirochete *Borrelia burgdorferi* sensu lato complex (*B. burgdorferi*) is the most frequent tick-borne central nervous system (CNS) infection in Europe with incidence rates estimated to be 3.2-6.3 per 100,000/year[1-7].

Typical symptoms of early European LNB include painful meningoradiculitis and facial palsy (called Bannwarth syndrome). Rarely, it presents in the third stage as chronic meningitis or chronic progressive encephalomyelitis[8].

Currently there is an unmet need for a highly standardized, minimally invasive biomarker test to monitor treatment response in LNB. Indeed, the relatively high frequency of persistent symptoms after the end of antibiotic treatment (estimated 15-20%), the variable clinical course and the long-lasting *B. burgdorferi* antibodies makes it difficult to differentiate between active and past infection. Today, a lumbar puncture is needed to ensure decrease in CSF leukocyte content and CXCL13 as blood inflammatory markers, such as white blood cell count (WBC) and C-reactive protein (CRP), usually are within the normal range. Although lumbar puncture is a low-risk procedure it is often uncomfortable and labor intense, thus avoiding this procedure will greatly improve disease monitoring.

Neurofilament light chain (NfL) is a biomarker of neuronal damage[9]. Neurofilaments are intermediate filaments of the neuronal cytoskeleton and highly expressed in large-caliber myelinated axons[9,10]. Conditions associated with axonal injury or degeneration in the nervous system leads to increases in the concentrations of NfL in CSF and blood[11]. We have previously found NfL to be elevated in most patients at diagnosis and to accurately reflect disease burden in LNB[12].

Objective

The objective of this study was therefore to evaluate plasma NfL as a biomarker for disease activity in LNB.

Methods

Study design

Prospectively included observational cohort study. Samples were analyzed retrospectively.

Setting

The study was initiated at the Department of Infectious Diseases at Rigshospitalet, University Hospital of Copenhagen, in January 2018. The study included adult (≥18 years) patients with definite European LNB diagnosed according to the European guidelines [25]. The patients were prospectively enrolled within one day before antibiotic initiation and up to 7 days after ended antibiotic therapy.

The patients were assessed at the Department of Infectious Diseases, Rigshospitalet, Denmark, from the 1st of September 2018 to the 31st of July 2020. Follow-up included clinical assessment and blood samples three months and six months after the time of diagnosis. To assess the clinical outcome, we used The Glasgow Outcome Scale (GOS). GOS 1=death; GOS 2=neurovegetative state; GOS 3=severe disability, GOS 4=moderate disability, GOS 5=good recovery. Laboratory analyses of blood and cerebrospinal fluid (CSF), baseline characteristics, and clinical findings were retrieved from a quality assessment database these included symptomatology, Charlson comorbidity index (CCI) and paraclinical data including routine blood biochemistry. Plasma samples were analyzed for NfL concentration at the Clinical Neurochemistry Laboratory at the University of Gothenburg (Sahlgrenska University Hospital).

Ethical Statement

The study was granted permission by the Ethical Committee of the Capital Region of Denmark, (Journal number H-19027317) and the Regional Data Protection Center of the Capital Region, Denmark (P-2019-707).

Participants

Patient with definite LNB diagnosed or referred to the Department of Infectious diseases, University hospital Copenhagen- Rigshospitalet from 1st of September 2018 to 31st of July 2020.

Definite LNB diagnosis was based on the presence of three criteria: (i) typical neurological symptoms, (ii) CSF leucocytes $\geq 10 \times 10^6$ cells/L, and (iii) a positive intrathecal *B. burgdorferi* antibody production index [13].

The IDEIA flagella antigen-based enzyme-linked immunosorbent assay LNB test (Oxoid Hampshire, United Kingdom) was used for detection of intrathecal synthesis of *B. burgdorferi.*-specific IgG and IgM antibodies [14]. An antibody production index >0.3 was considered as positive according to the manufacturer's instructions.

Symptom duration:

Onset of LNB was defined as the onset of neurological symptoms and the duration of neurological symptoms was defined as the number of days from onset of neurological symptoms to diagnostic lumbar puncture.

Symptoms and signs of LNB:

The following symptoms were registered: radiating pain, fever, headache, chronic headache (duration for more than 6 months), peripheral cranial nerve palsies (nerve III, VI or VII), uni- or bi-lateral cranial nerve palsy, limb palsies (upper, lower extremities, hemi- or paraparesis), consciousness, sensory disturbances, gait disturbances, stroke (MRI verified), cognitive complaints, seizures, vomiting, encephalopathy or other (free text).

Time from treatment initiation was counted in days from first dose of relevant antibiotic treatment. Baseline or at treatment initiation was considered day 0-24, 3-months control day 67-137 and 6-months day 149-413.

Variables

The main outcome variable in this study was pNfL (pg/mL). pNfL was measured consecutively at diagnosis, 3- and 6-months follow-up.

Age-defined reference were 5-17 years = 7 pg/mL; 18-50 years = 10 pg/mL; 51-60 years = 15 pg/mL; 61-70 years = 20 pg/mL; 70+ years = 35 pg/mL. Based on *Simren et al* (unpublished).

Measurement

pNfL was measured using the Simoa® HD-X or HD-1 analyzers according to the manufacturer's instructions (Quanterix®, Billerica, MA, USA). Samples were run in singlicates and each assay plate included internal quality control (QC) samples with high and low pNfL concentrations, respectively, analyzed in duplicate both in the beginning and end of the plate.

Glasgow outcome scale-Extended (GOS): rated from 1 to 5, described above

Bias

This cohort included only patients with definite LNB which may have introduced a selection bias. GOS scores were only available for a subset of 25 individuals.

Study size

Given a power of 0.8 and type 1 error rate of 0.05 and a hazard ratio of 2 and probability of event to be 1, the sample size was calculated to be 33.

Quantitative variables

p-NfL was the main quantitative variable. Age-defined reference were 5-17 years = 7 pg/mL; 18-50 years = 10 pg/mL; 51-60 years = 15 pg/mL; 61-70 years = 20 pg/mL; 70+ years = 35 pg/mL. Based on *Simren et al* (unpublished). Within each age category (grouping) the variable was regarded as pathologically elevated if above the age-defined reference.

Statistical methods

Descriptive statistics are given in median values and interquartile ranges. For comparisons over time Wilcoxon matched pairs signed ranked test and a two-way ANOVA test was applied, p-values under 0.05 was considered significant. Simple linear regression was performed to test correlation. Mann-Whitney was used to test differences between variables.

Statistical test was performed using the GraphPad PRISM version 9.0.0 (GraphPad Software, LLC).

Relative change from the age defined reference of pNfL was derived by (relative change from reference= (actual pNfL value – age defined reference of pNfL)/age defined reference pNfL)

Results

Participants

A total of 36 patients with definite LNB were prospectively included in the study.

Descriptive Data

Baseline characteristics and pNfL values are listed in Table 1, further details on clinical and paraclinical information are listed in supplementary table 1.

Median age was 63 years (Inter Quartile Range (IQR) 54-71). There was a slight overweight of male sex (64%). Over half of patients reported a tick bite and 38% had a history with erythema migrans. Median comorbidities as defined by the Charlson Comorbidity Index was 2. Median symptom duration at diagnosis was 30 days (IQR 19-60). Most presented with radiating pain (97%), cranial nerve palsies (42%) and limb palsies (39%), while 5% suffered chronic CNS symptoms.

Twenty of the 36 patients (56%) reported sequelae at 6 months follow-up. The most frequent complaint was pain (12/20), followed by residual palsy (6/20), fatigue (5/20) and cognitive complaints (4/20).

For a subset of 25 individuals, consecutive GOS were available. Significant improvement from treatment initiation to 3 months follow-up was observed (median 4 (IQR 3-4) vs median 4 (IQR 4-5)), p=0.01. The increase in GOS from 3 to 6 months follow-up, was not found to be significant (median 4(IQR 4-5) vs median 5(IQR 4-5)), p=0.25. (Wilcoxon matched-pairs signed rank test).

GOS scores are illustrated in Figure 1.

Outcome data and main results

Plasma NfL significantly decreases following antibiotic treatment

Plasma NfL as a function of days from treatment initiation is illustrated in Figure 2. A significant decline in pNfL was observed from baseline to 3- and 6 months follow-up (median 83 pg/ml vs median 14 pg/ml (25 pairs), p<0.0001 and median 83 pg/ml vs median 12 pg/ml (24 pairs), p<0.0001). However, no significant difference was observed between 3 and 6 months (median 14 pg/ml vs median 12 pg/ml (21 pairs), p=0.33) (Wilcoxon matched-pairs signed ranked test). The reduction of pNfL over time was also explored by ANOVA and found to be significant (p<0.0001).

Ninety percent had elevated pNfL at treatment initiation, followed by 23% at 3 months and 7% at 6 months (Figure 3). In the two individuals with pNfL above reference at the 6 months follow-up, a

significant decrease in pNfL from baseline was observed (from 19.0 and 739.0 pg/mL respectively to 16.7 and 25.0 pg/mL respectively). Thus, pNfL at the 6 months follow-up was only marginally above the age defined reference of 15 and 20 pg/mL, respectively.

Three patients did not have elevated pNfL values at diagnosis, one (PID 8416) was diagnosed very early (7 days after onset of symptoms), whereas the remaining 2 (PID 8420 and 8435) had had symptoms for 21 and 50 days at treatment initiation, respectively. Main symptoms in PID 8420 peripheral facial nerve paresis and fatigue. Main symptoms in PID 8435 were lower backpain radiating to lower extremities and sensory disturbances in left foot.

The greatest relative change in pNfL to the reference was observed from treatment initiation to 3 months control. Here, the median relative change from the age defined reference went from a median change of 1.17 pg/ml (IQR 0.22-7.2) to -0.325 (IQR -0.57—0.04). Little or no change was observed between the 3- and 6 months follow-up (-0.325 (IQR -0.57—0.04) to median -0.49 (IQR -0.61—0.14), illustrated in Figure 4. Pathologic values of pNfL were rarely observed 100 days after the initiation of treatment.

Association between age and pNfL correlated restored at 3- and 6 months follow-up

NfL is known to naturally increase with age as a reflection of age-related neuronal injury. At baseline we found this association to be disrupted, tested by simple linear regression (R squared 0.05, p=0.19) but restored at the 3- and 6- months follow-up (R squared 0.17, p=0.04 and R squared 0.29, p=0.01, respectively), reflecting a normalization of pNfL. Data not shown.

Reporting persistent symptoms was not associated with pNfL at baseline or follow-up.

Although all patients in this study were successfully treated, 20 of 36 reported persistent symptoms at the 6 months follow-up. The most frequent complaint was pain (12/36), followed by palsies (6/36), fatigue (5 of 36) and cognitive difficulties (4/36).

Reporting persistent symptoms at the 6 months follow-up was not associated with having higher pNfL (higher relative change from reference or actual values) at baseline or at 6 months follow-up (data not shown).

Significant association between CSF total protein and pNfL at baseline, but not CSF leukocytosis

A significant association between the level of CSF total protein and the relative change in pNfL from reference at baseline (p=0.0001, R squared 0.37) was found whereas there was no association between CSF leukocytosis and pNfL (p=0.17, R squared 0.06).

Discussion

Key results

In prospectively included patients with definite LNB, we found pNfL to be elevated above the age defined reference in most individuals at diagnosis. Following antibiotic treatment pNfL decreased in all individuals and was rarely above reference at follow-up. Decreasing pNfL was mirrored by increasing GOS but not associated with reporting residual symptoms. We therefore speculate that pNfL may be useful in monitoring treatment response in LNB patients.

Increases in concentrations of NFL in cerebrospinal fluid, serum and plasma have been observed in a wide range of diseases and is thought to be useful as a general measure of injury to neurons and axons in the peripheral and the central nervous system[15,16]. In multiple sclerosis (MS), there is compelling evidence that CNS inflammation leading to demyelination and neuroaxonal injury is accompanied by increases in CSF and blood concentrations of NfL, and that immunomodulatory treatments that reduce relapses and disease activity on magnetic resonance imaging also reduces concentrations of NfL[17,18].

Although we did not have more frequent monitoring than at 3- and 6 months follow-up the dynamics of pNfL in this study seem to be in line with what is observed in MS, although the underlying pathophysiology is quite different. We speculate that pNfL is a good reflection of the decreasing CNS inflammation following antibiotic-induced spirochete killing. Spinal tapping was only performed at treatment initiation in this study, but previous studies with serial lumbar punctures have shown normalization of CSF 3-4 months after treatment initiation[19]. It will be interesting to obtain more detailed information on decay patterns following antibiotic treatment in LNB. As not all patients had normalized pNfL values at the 3 months follow-up, reduction in pNfL from treatment initiation may prove more informative than a single measurement to evaluate treatment response.

Serum NfL is influenced by age, BMI, glycosylated hemoglobin (a biomarker of diabetes mellitus), kidney function and neurodegenerative diseases, therefore caution should be taken when interpreting p/sNfL in this context[20,21]. In our study, patients all had normal kidney function, none had diabetes or BMI over 25.

The pathogenesis of persistent symptoms related to LNB is currently unclear although the phenomenon is well documented [22] and most often consists of pain, fatigue, cognitive impairments, and neurological sequelae in the form of residual paralysis. Plasma NfL was not associated with having persistent symptoms in this study, suggesting that the pathogenesis may be different from active infection.

In conclusion, although pNFL is an unspecific marker, reflecting neuron damage in general, we speculate that a measure compared to initial values taken at treatment initiation may serve as a biomarker for treatment response without having to perform a lumbar puncture.

Limitations

The study size was relatively small and only patients with definite LNB were included. We are thus not certain if our observations hold true for probable or early LNB. Consecutive spinals taps were not performed thus it is unknown how strongly pNfL correlates to CSF inflammation after treatment initiation. None of the patients were suspected to have treatment failure and none of the patients had had LNB previously thus uncertainty exist as to how pNfL will behave in these situations. pNfL was measured with 3 months intervals and thus we do not have data to support pNfL as a biomarker earlier than 3 months after treatment initiation.

Interpretation

The level of plasma NfL reflects acute neuroaxonal damage in LNB and could prove useful as a blood marker for treatment response in LNB.

Generalizability

Borrelia burgdorferi sensu lato genospecies are restricted in geographical occurrence and organotropism. European LNB is associated with B. Garinii infection. Currently, it is unknown if our finding holds true for North-American LNB and other neuroinfectious.

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Characteristics total cohort (N=36)	No. (%) or median (IQR)
Age, years	63(54-71)
Male sex	23(64%)
Symptom duration at diagnosis (days)	30(19-60)
Recollection of tick bite	24/36 (67%)
History with erythema migrans	14/36 (39%)
Charlson comorbidity score	0(0-1)
Symptoms	
Peripheral cranial nerve palsy	15/36 (42%)
Nerve VII	14/15 (93%)
Nerve III	1/15 (7%)
Nerve V	0/15 (0%)
Limb paresis	14/36 (39%)
Radiating pain	35/36 (97%)
Chronic CNS symptoms	2/36 (5%)
Plasma NfL	
NFL (pg/mL) at diagnosis (N=29) (0-24 days)	83(42-179)
NFL above reference at diagnosis	26/29 (90%)
NFL at 3 months (day 44-137) (N=26)	15(9-21)
NFL above reference at 3 months	6/26 (23%)
NFL at 6 months (day 149-413) (N=25)	13 (8-16)
NFL above reference at 6 months	2/25 (8%)
Number of samples per patient	3(2-3)

Figure 1.

Stacked bar chart showing changes in Glasgow Outcome Score (GOS) at diagnoses, 3- and 6-months follow-up. GOS of 1 in light blue, GOS of 2 in purple, GOS of 3 in pink, GOS of 4 in green and GOS of 5 in dark blue

Figure 2.

Line chart with plasma Neurofilament Light (in pg/mL) plottet against time (days from treatment initiation). Each line represent individual patient data.

Figure 3.

Stacked bar chart illustrating the percentage of patients at baseline, 3- and 6-months follow-up with plasma Neurofilament Light chain (NfL) within reference (light gray) and above reference(dark gray)

Figure 4.

Column scatter graph illustrating the relative change in plasma neurofilament Light (in pg/mL), (from the age defined reference at baseline, 3-months and 6-months follow-up (relative change from reference= (actual pNfL value – age defined reference of pNfL)/age defined reference pNfL))

Table 1:

Clinical characteristics and concentration of plasma-neurofilament light (p-NfL) at 3 timepoints in 36 patients with definite Lyme neuroborreliosis (LNB).

IQR; interquartile range, CNS; central nervous system