



CXCL13 in patients with facial palsy caused by varicella zoster virus and *Borrelia burgdorferi*: a comparative study

Johan Lindström^{a,b,*}, Daniel Bremell^{a,b}, Anna Grahn^{a,b}, Kaj Blennow^{c,d}, Henrik Zetterberg^{c,d,e,f}, Marie Studahl^{a,b}

^a Department of Infectious Diseases, Sahlgrenska University Hospital, Gothenburg, Sweden

^b Department of Infectious Diseases, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Sweden

^c Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden

^d Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden

^e Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK

^f UK Dementia Research Institute at UCL, London, UK

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ABSTRACT

High cerebrospinal fluid (CSF) concentrations of the chemokine CXCL13 have been associated with Lyme neuroborreliosis (LNB), and have recently been studied as a potential diagnostic marker. It has proven difficult to establish a reliable diagnostic cut-off, possibly in part due to heterogeneity of case-control groups. Our purpose was to investigate CSF CXCL13 concentrations in patients with similar clinical presentations, facial palsy. We retrospectively included patients with facial palsy associated with LNB ($n = 21$), or varicella zoster virus (VZV) ($n = 26$). Median CXCL13 concentrations were significantly higher in patients with LNB facial palsy compared to VZV facial palsy. Receiver-operating characteristic analyses yielded an optimal cut-off concentration at 34.5 pg/mL (sensitivity 85.7%, specificity of 84.6%), lower than that in previous studies. Although the analysis has potential, it is still not adequately established that CXCL13 provides additional, clinically useful, diagnostic information over current recommendations.

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1. Background

Lyme neuroborreliosis (LNB) is a central nervous system (CNS) infection caused by the arthropod-borne spirochete *Borrelia burgdorferi* (*Bb*). According to European guidelines, a definitive diagnosis of LNB requires a combination of typical clinical symptoms, pleocytosis in the cerebrospinal fluid (CSF) and positive *Bb* antibody index as evidence of intrathecal antibody production (Mygland et al., 2010). Unfortunately, there are several limitations to this definition. Antibody production can be undetectable up to 6 weeks from emergence of symptoms, and can persist for several years after initial disease (Hansen and Lebech, 1992; Hammers-Berggren et al., 1993). Consequently, diagnosis of both early LNB and suspected reinfection is problematic, as the presence of lymphocytes in the CSF is non-specific to LNB.

In an effort to improve diagnostics in CNS infections, high concentrations of the chemokine CXCL13 in CSF has emerged as a possible marker of LNB (Rupprecht et al., 2005). CXCL13, also known as B lymphocyte chemoattractant, is likely important as part of the immune response

in LNB (Rupprecht et al., 2009). CXCL13 is produced in the CNS in a rapid response to infection, and is detectable before antibodies are present (Senel et al., 2010).

An increasing number of studies have reliably detected significantly higher concentrations of CXCL13 in CSF from patients with LNB compared to other CNS infections and inflammatory diseases (Rupprecht et al., 2005; Ljostad and Mygland, 2008; Senel et al., 2010; van Burgel et al., 2011; Barstad et al., 2017), and it has also been shown that concentrations decline after treatment (Senel et al., 2010; Schmidt et al., 2011; Bremell et al., 2013). Exceptions where similarly increased concentrations may be seen are cryptococcosis, neurosyphilis, tuberculous meningitis and CNS lymphoma (Rupprecht et al., 2009; Marra et al., 2010; Schmidt et al., 2011; van Burgel et al., 2011; Rubenstein et al., 2013). In some of the studies, analyses have been performed with receiver operating characteristic (ROC) analyses, yielding a variety of suggested cut-off concentrations for CSF CXCL13, ranging from 18 pg/mL (Barstad et al., 2017) to 1224 pg/mL (Schmidt et al., 2011). In a recently published meta-analysis by Rupprecht et al. (Rupprecht et al., 2018), including 18 studies, a CSF CXCL13 cut-off at 162 pg/mL was found optimal, at a pooled sensitivity of 89% and a specificity of 96%, or if only including cross-sectional studies, 91 pg/mL.

* Corresponding author. Tel.: +46313439316; fax: +4631847813.

E-mail address: johan.lindstrom@gu.se (J. Lindström).

There is no established reference method for CXCL13, so there may be method-related explanations for the varying cut-off concentrations (Henningsson et al., 2016), although several of the studies use the same commercial kit in their analyses. In addition, the patients included in previous studies have presented with a variety of clinical syndromes and duration of symptoms before sampling, which raises questions on comparability.

Facial palsy is a common manifestation of LNB, but can also be caused by varicella zoster virus (VZV) reactivation, traditionally named Ramsay Hunt syndrome (RHS) (Sweeney and Gilden, 2001). Improved diagnostics, such as detection of VZV DNA by PCR of patient CSF, enables patients to be diagnosed with VZV facial palsy regardless of the presence of blisters associated with classical RHS. In the patient with facial palsy, the clinical presentation including associated symptoms may be non-specific, making it impossible to distinguish VZV facial palsy from LNB facial palsy before the results of etiological diagnostics are available. Additionally, CSF pleocytosis is present in both conditions, and in the case of LNB, antibody production may be absent if the duration of symptoms is short. A comparison of CSF CXCL13 in such similar and relevant patient groups has so far not been performed.

2. Patients and methods

Patients

A total of 21 patients with peripheral facial palsy associated with LNB were included from two patient cohorts previously included in unrelated prospective studies on LNB (Bremell and Hagberg, 2011). All patients were examined at the Department of Infectious Diseases, Sahlgrenska University Hospital, Gothenburg, Sweden, between 2000 and 2013, and had a lumbar puncture performed before the initiation of antibiotic treatment. Diagnostic criteria for LNB were: peripheral facial palsy, mononuclear pleocytosis in CSF (>5 cells/ μ L) and Borrelia-specific intrathecal antibody production in CSF demonstrated with a positive CSF/serum antibody index (AI), in accordance with European Federation of the Neurological Societies (EFNS) guidelines (Mygland et al., 2010). Patients fulfilling 2 out of 3 criteria are defined as possible LNB according to EFNS guidelines. Since peripheral facial palsy may be present before development of Borrelia-specific antibodies, a history of erythema migrans within 3 months before onset of neurological symptoms was also considered diagnostic in absence of a positive CSF/serum antibody index.

Twenty-six patients with VZV facial palsy were obtained from a related study on other CSF biomarkers (Lindstrom et al., 2016). These patients were retrospectively identified by detection of VZV DNA in CSF by quantitative in-house PCR, through CSF samples sent to the Virological Laboratory of Sahlgrenska University Hospital during 2002–2013. Subsequently, facial palsy was identified in medical records, and patients with other coexisting CNS diseases were excluded.

As a control group, CSF samples from 52 subjects presenting with headache or psychoneurotic symptoms were used. Controls did not have 1) increased lymphocyte counts or protein concentrations in the CSF, 2) concomitant CNS disease or CNS disease identified within 1 year after sampling, 3) increased C-reactive protein concentrations in blood, or 4) pathological findings at neurological examination.

2.1. CSF samples and analyses

Two different tests were used to analyze Bb-specific antibodies in CSF and serum during the study period. Until June 26, 2006, samples were analyzed for IgG and IgM with the Dako Lyme Borrelia ELISA kit using purified native *B. burgdorferi* flagellum as antigen (Dako Cytomation A/S, Glostrup, Denmark). From June 26, 2006, samples were analyzed with the Liaison chemoluminescence immuno-assay (CLIA), using recombinant VlsE as antigen for IgG and recombinant OspC as antigen for IgM (Diasorin, Saluggia, Italy). Cut-off values for positive samples were according to the manufacturers' instructions.

Until June 26, 2006, the Bb-antibody index was calculated using the optical density (OD) values from the Dako Lyme Borrelia ELISA test using the formula $(OD\text{-CSF}/OD\text{-serum}) \times OD\text{-CSF} - OD\text{-serum}$ where antibody index values >0.3 were considered positive (Hansen and Lebech, 1991). From June 26, 2006, Bb-antibody index was calculated as the ratio of the CSF/serum quotient of specific antibodies to the corresponding CSF/serum quotient of total immunoglobulins as described by Reiber and Lange. Antibody index values >1.4 were considered positive (Reiber and Lange, 1991).

VZV DNA analysis of CSF samples, with a detection limit of 100 copies/mL, was performed by quantitative in-house PCR previously described (Persson et al., 2009), as part of diagnostic procedure of symptoms.

CXCL13 was measured in stored CSF samples by ELISA (R&D Systems) according to manufacturer recommendations, with a lower limit of quantification of 7.8 pg/mL. CSF samples from patients with VZV facial palsy had been stored at -70°C or -20°C . CSF samples from control subjects and LNB patients had been continually stored at -70°C as part of a biobank where procedures include dividing CSF samples into smaller aliquots to eliminate the need for thawing and refreezing.

2.2. Statistics

Statistical analysis was performed using Graphpad Prism 8.4.1 (GraphPad Software, San Diego, USA). CXCL13 values under the detection limit of 7.8 pg/mL were assigned a value of 3.9 pg/mL for graphical purposes. Mann–Whitney *U* test was used for comparison between the 2 groups with LNB facial palsy and VZV facial palsy, Kruskal–Wallis test for comparisons including the control group. Receiver operating characteristic (ROC) curve analysis was performed, using the Youden index (sensitivity+specificity–1) to define optimal cut-offs. Numbers are presented as median and range unless otherwise is indicated.

2.3. Ethics

The Regional Ethical Review Board at the University of Gothenburg approved the study (Dnr 385–95 and 664–13).

3. Results

3.1. Patient and control characteristics

Patient and CSF characteristics are shown in Table 1. Out of the 21 patients with LNB and peripheral facial palsy, all but one patient fulfilled EFNS criteria for definitive LNB. One patient, who had not developed specific antibodies, had a recent history of erythema migrans.

Table 1

Clinical data and CSF findings of the included patients with LNB facial palsy, VZV facial palsy, and controls.

	LNB (n = 21)	VZV (n = 26)	Controls (n = 52)	P value
Sex M/F	10/11	14/12	22/30	
Age (years)	55 (7–74)	60 (17–93)	60 (16–87)	0.64
Symptom duration (days)	4 (1–35)	2 (–9–57)		0.034
CSF cell count (no/ μ L)	153 (17–722)	105 (3–588)		0.28
CSF protein (mg/L)	839 (267–2850)	412 (124–1000)		0.0016
Time in freezer (years)	6 (1–14)	2.5 (1–12)		0.011
CXCL13 (pg/mL)	2041 (22–36,924)	8.5 (<7.8–437)	<7.8 (<7.8–9)	<0.0001

LNB = Lyme neuroborreliosis; VZV = Varicella zoster virus. Comparisons were made using the Mann–Whitney *U* test when comparing the LNB and VZV groups, Kruskal–Wallis test for comparisons including the control group.

Sex and age distribution were similar in patients with LNB (10 females and 11 males; median age 55, [range 7–74]), in patients with VZV facial palsy (12 females and 14 males; median age 60 years [7–93]) and in control subjects (30 females and 22 males; median age 60 years [16–87]) ($P = 0.64$).

Median number of days between debut of facial palsy and CSF sampling was 4 [range 1–35] for LNB patients and 2 [range –9 to 10] for VZV patients ($P = 0.034$). There was no significant difference in CSF cell count between LNB patients (median 153/ μL [range 17–722]) and VZV patients (105/ μL [range 3–588]) ($P = 0.28$), but CSF protein was significantly higher in CSF from LNB patients (839 mg/L [267–2850]) compared to VZV patients (412 mg/L [124–1000]).

Localized pain or headache was frequent in both the LNB group (11/21) and the VZV facial palsy group (26/26), but neurological symptoms outside of the facial area was more prevalent in the LNB group compared to the VZV group, and included typically radicular pain ($n = 11/26$). In addition, 14/26 of the patients with VZV facial palsy had blisters, most commonly in the ipsilateral ear region, 16/26 had vertigo and 16/26 had affected hearing. Two VZV patients were encephalitic and two patients had mild upper limb paresis but no radicular pain.

3.2. CSF CXCL13 concentrations

Median CSF concentrations of CXCL13 for facial palsy caused by LNB were 2041 pg/mL (range 22–36,924), for VZV facial palsy 8.5 pg/mL (range <7.8–437); only in one control sample, CXCL13 concentration exceeded the detection limit with a concentration of 9.0 pg/mL (Fig. 1).

The differences in CXCL13 concentrations between patients with LNB facial palsy and VZV facial palsy were highly significant ($P < 0.0001$).

ROC analyses were performed on the LNB and VZV facial palsy groups to find an optimal cut-off concentration for CXCL13. A cut-off concentration of 34.5 pg/mL yielded a sensitivity of 85.7% and a specificity of 84.6% (Fig. 2a). Limiting the analysis to patients who had undergone lumbar puncture within the first week after debut of facial palsy (13 LNB, 20 VZV), a cut-off concentration of 86 pg/mL yielded a sensitivity of 92.3% and a specificity of 90% (Fig. 2b).

The only LNB patient without a positive antibody index had a markedly increased CXCL13 of 17,446 pg/mL. Five patients fulfilling the criteria for definite LNB had CXCL13 concentrations lower than 50 pg/mL. In four of these cases, CSF had been stored for more than 10 years before analysis, and in three of these cases the duration of facial palsy was 2 weeks or more before sampling was performed. In one patient with a CXCL13 of 35 pg/mL, sampling was performed 4 days after debut of facial palsy, and serological examination was highly positive for

intrathecal *Borrelia*-specific antibody production. No antibiotic treatment had been given prior to CSF sampling.

Only two patients with VZV facial palsy had CXCL13 increases above 100 pg/mL. First, one 82-year-old female with a CXCL13 of 437 pg/mL who was admitted with vertigo and after 5 days in-hospital developed facial palsy and blisters typical of zoster oticus. She reported infection with *Borrelia* 7 years earlier, and *Borrelia* antibodies were detected in serum but not in the CSF. VZV infection was confirmed through PCR of CSF. Second, one otherwise healthy 29-year-old male who presented in April of 2006, outside of the normal tick-bite season, with typical zoster oticus including associated blisters. Since VZV infection was confirmed through PCR of CSF, no *Borrelia*-specific analyses were performed. CXCL13 was increased at 142 pg/mL.

4. Discussion

In this first comparative study on CXCL13 in patients with facial palsy caused by LNB and VZV, we can confirm significantly higher concentrations of CXCL13 in the CSF of patients with LNB compared to patients with reactivated VZV.

However, the optimal cut-off concentrations for CXCL13 according to the meta-analysis by Rupprecht et al. (Rupprecht et al., 2018) would lead to unacceptably low sensitivity in our material. A cut-off at 162 pg/mL corresponds to a sensitivity of 71.4% including all our patients, if we only include patients where sampling was performed in the first week after debut of facial palsy, the sensitivity increases to 84.6%, both with a specificity over 90%. When performing the ROC analyses, our intention was to further show the diversity in CSF CXCL13 expression, and to highlight the difficulties in establishing a reliable cut-off, rather than proposing one of our own. More than half the patients with VZV facial palsy had increased concentrations of CXCL13, weakening specificity of the analysis, but the main finding of low sensitivity for diagnosing LNB using the proposed cut-offs, is related to the relatively low increase of CXCL13 in the CSF from our LNB patients.

There could be multiple explanations to the relatively low increases of CXCL13 shown in the CSF of some of our patients compared to other studies. Selecting patients primarily based on antibody index suggests that enough time has passed since time of infection to allow the immune response to produce antibodies, potentially downstream from early infection where the highest concentrations of CXCL13 are detected (Senel et al., 2010). Isolated facial palsy as a symptom may also have a lesser potential to induce the inflammatory response, being more localized, compared to a more widespread infectious process in the CNS. An additional consideration is time from sampling to analysis in a retrospective study such as ours. There are indications that CXCL13 may degrade over time (Schmidt et al., 2011), and in some cases our samples had been stored for up to 14 years. However, in one study, storage of CSF samples in $-20\text{ }^{\circ}\text{C}$ for up to 5 years did not result in significantly lower concentrations (van Burgel et al., 2011), and in another study, when the same CSF sample was divided and freeze-thawed up to 5 times, CXCL13 concentrations were unaltered (Hytonen et al., 2014). Although our findings of low increases in CSF CXCL13 are unusual, similar results have been previously described. In Barstad et al. (Barstad et al., 2017) 4/59 children with definite LNB had CSF CXCL13 concentrations <81 pg/mL, and in Picha et al. (Picha et al., 2016) 3/44 adults with definite LNB had CSF CXCL13 concentrations <131 pg/mL. Regardless, the results suggest that methods for measuring this biomarker should be harmonized and, preferably, standardized to a certified reference material.

The results from the present study indicates that analysis of CSF CXCL13 may be of use in the differential workup of patients presenting with facial palsy, although there is still uncertainty regarding optimal cut-offs and applicability. Additionally, studies on CSF CXCL13, including ours, have been performed almost exclusively on European patients, and differences in clinical presentations as well as *Borrelia* subspecies makes it difficult to draw conclusions regarding CSF CXCL13 in other

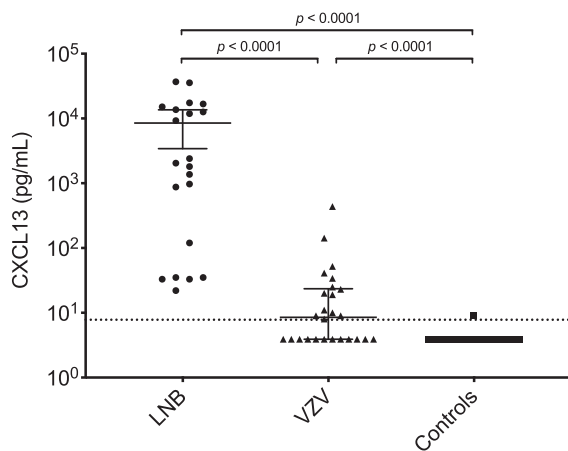


Fig. 1. CXCL13 concentrations in CSF of patients with facial palsy caused by LNB ($n = 21$) compared to VZV ($n = 26$) and controls ($n = 52$) (individual concentrations, median and quartiles).

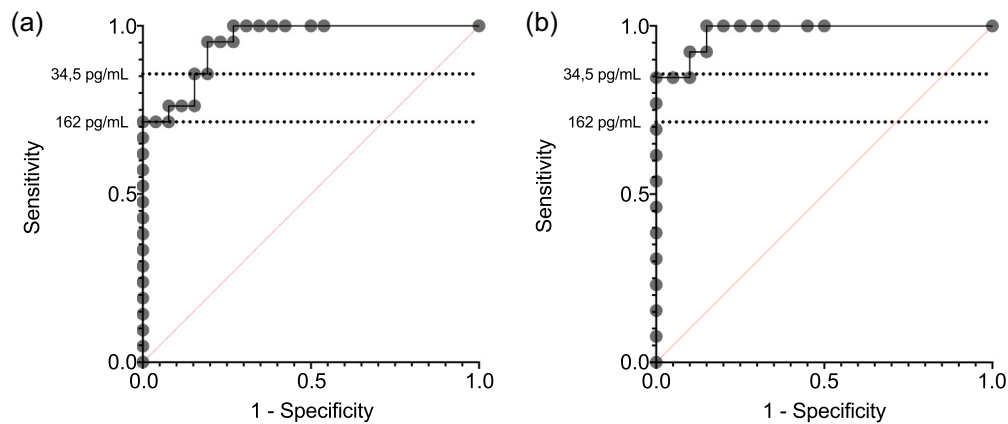


Fig. 2. Receiver-operating characteristic (ROC) curves of CSF CXCL13 concentrations from patients with facial palsy caused by LNB ($n = 21$) versus VZV ($n = 26$). The upper horizontal line indicates the optimal cut-off in our material according to Youden index, the lower horizontal line indicates the proposed cut-off from Rupperecht et al. (2018) (a) ROC including all patients. (b) ROC including LNB ($n = 13$) and VZV ($n = 20$) patients sampled within 1 week of debut of symptoms.

geographic settings. The added value of the CXCL13 analysis might be in patients who have not yet developed CSF pleocytosis and/or antibody response to *Borrelia* due to the short duration of their illness, or in patients with a previous history of LNB, as positive AI may persist for years (Hansen and Lebech, 1992; Hammers-Berggren et al., 1993). In our study, all but one patient had a positive AI only days after debut of facial palsy, implicating that it is a symptom that may develop relatively late in LNB. In addition, according to current EFNS guidelines for possible LNB (Mygland et al., 2010), many patients are prescribed antibiotics when CSF cell count is found to be positive, before the results from the antibody analysis are available. As such, the added benefit of CXCL13 would be to avoid unnecessary antibiotic prescriptions and move focus to potential differential diagnoses. In a newly published study by Pietikäinen et al. (Pietikäinen et al., 2018), the authors advocate for a new CXCL13 lateral flow assay, suitable for point-of-care testing. Such an assay could potentially widen the indication for CXCL13 testing, and have an impact on clinical practice.

Even if CSF CXCL13 has potential as a useful analysis in the clinical setting, further studies on CNS infections with similar clinical presentations are warranted, primarily focusing on patients only fulfilling the criteria of possible LNB, where the potential added diagnostic value is greatest.

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Declaration of competing interest

HZ has served at scientific advisory boards for Roche Diagnostics, Samumed, CogRx and Wave, has given lectures in symposia sponsored by Biogen and Alzecure, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg (all outside submitted work). KB has served as a consultant or at advisory boards for Biogen, Lilly, Novartis and Roche Diagnostics, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Venture-based platform company at the

University of Gothenburg, (all outside submitted work). The other authors report no conflicts of interest.

Author Statement

Johan Lindström: Methodology, Formal analysis, Writing- Original draft preparation, Visualization. **Daniel Bremell:** Investigation, Methodology, Writing- Reviewing and Editing. **Anna Grahn:** Investigation, Writing- Reviewing and Editing. **Kaj Blennow:** Resources, Validation, Writing- Reviewing and Editing. **Henrik Zetterberg:** Resources, Investigation, Validation, Writing- Reviewing and Editing. **Marie Studahl:** Conceptualization, Supervision, Writing- Reviewing and Editing.

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