

CSF examinations for diagnosis and treatment of Lyme neuroborreliosis

PD Dr. T. Rupprecht

Lyme neuroborreliosis – classification



European Journal of Neurology 2009

doi:10.1111/j.1468-1331.2009.02862.x

EFNS GUIDELINES

EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis

Å. Mygland^{a,b,c}, U. Ljøstad^a, V. Fingerle^d, T. Rupprecht^e, E. Schmutzhard^f and I. Steiner^g

Table 1 Classification of Lyme neuroborreliosis (LNB)

Early LNB

Neurological symptoms for < 6 months

With manifestations confined to PNS (cranial nerves, spinal roots or peripheral nerves) (Bannwarth syndrome)

With CNS manifestations

Late LNB

Neurological symptoms for more than 6 months

With PNS manifestations

With CNS manifestations

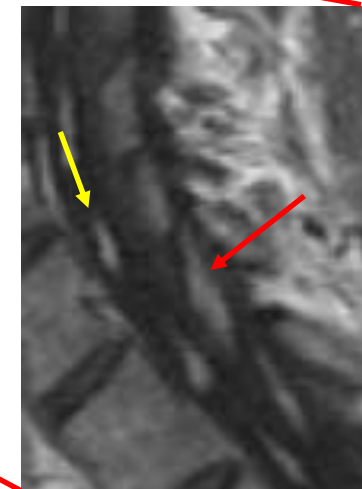
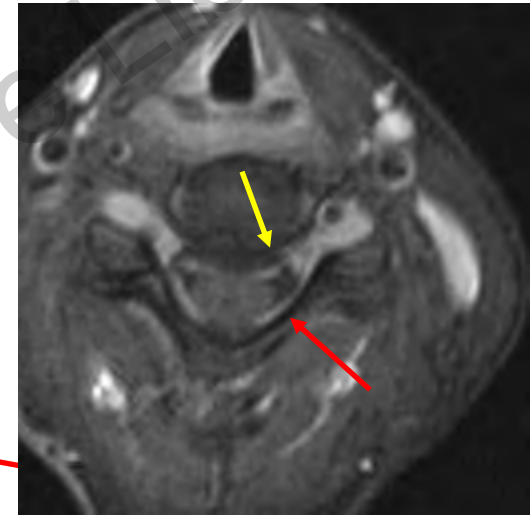
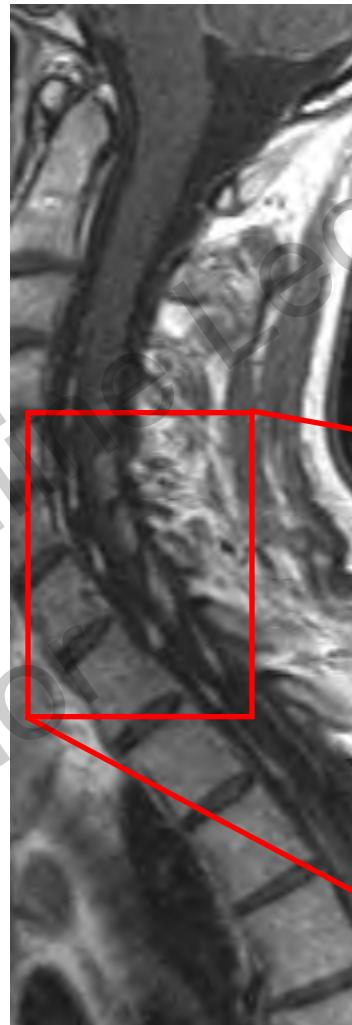
Early Lyme neuroborreliosis – Bannwarth's syndrome

Meningopolyradiculitis
(Bannwarth's syndrome)

⇒ spinal nerve roots:
pain (86%), palsy (61%)



palsy of the
abdominal muscles



Early Lyme neuroborreliosis – Bannwarth's syndrome

Meningopolyradiculitis (Bannwarth's syndrome)

⇒ spinal nerve roots:
pain (86%), palsy (61%)

⇒ cranial nerves:
palsy (50-60%)



Bilateral facial palsy



Palsy of the right N. abducens

Early Lyme neuroborreliosis – CNS manifestations

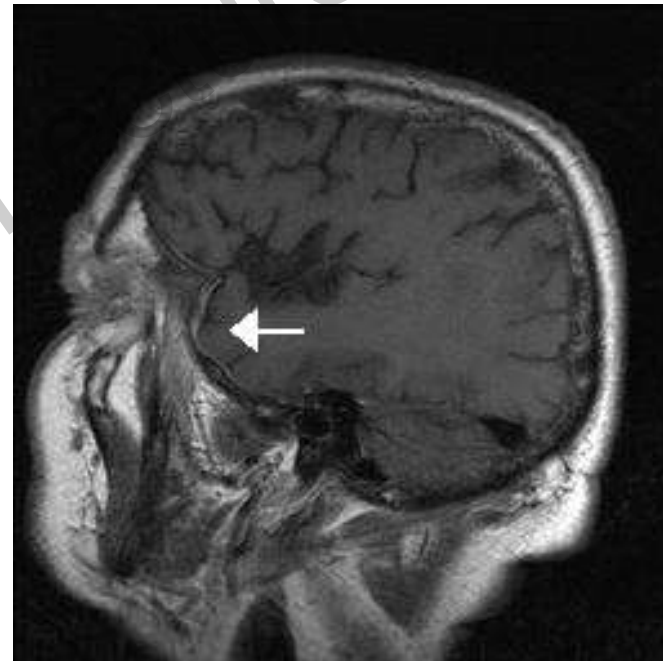


Meningitis
(>95% in combination with
Bannwarth's syndrome)

Myeloradiculitis (<2%)

Encephalitis (<1%)

Cerebral vasculitis (⇒ cerebral infarction)



Late Lyme neuroborreliosis – clinical presentation

PNS manifestation: Polyneuropathy

(only in association with
Acrodermatitis chronica atrophicans)



CNS manifestation: Encephalomyelitis



Suspected Lyme neuroborreliosis: Lumbar puncture obligatory!



European Journal of Neurology 2009

doi:10.1111/j.1468-1331.2009.02862.x

EFNS GUIDELINES

EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis

Å. Mygland^{a,b,c}, U. Ljøstad^a, V. Fingerle^d, T. Rupprecht^e, E. Schmutzhard^f and I. Steiner^g

Analysis of the
Cerebrospinal fluid (CSF):
Central point in the
Diagnosis of
Lyme neuroborreliosis!



Definite neuroborreliosis ^a	Possible neuroborreliosis ^b
All three criteria fulfilled	Two criteria fulfilled
Neurological symptoms suggestive of LNB without other obvious reasons	
Cerebrospinal fluid pleocytosis	
Intrathecal <i>Bb</i> antibody production	

^aThese criteria apply to all subclasses of LNB except for late LNB with polyneuropathy where the following should be fulfilled for definite diagnosis: (I) peripheral neuropathy (II) acrodermatitis chronica atrophicans (III) *Bb*-specific antibodies in serum.

^bIf criteria III is lacking; after a duration of 6 weeks, there have to be found *Bb*-specific IgG antibodies in the serum.

Lumbar puncture: the procedure

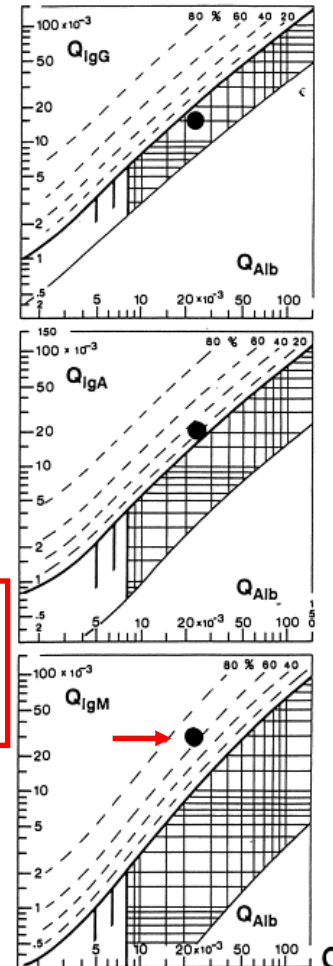


Lumbar puncture: the procedure



CSF analysis: the necessary basic parameters

- Cell count (CSF pleocytosis: 4-1,000 / μ l)
cell differentiation (lymphocytes, plasma cells)
- Total protein amount (0.2-12 g/l), Albuminratio
- IgG, IgA und IgM (IgM often predominates)
- Qualitative detection of oligoclonal IgG (except Q_{IgG} is $>Q_{Alb}$)
- Detection of **intrathecal**, borrelia specific antibody production (antibody index)
- search for bacteriae (PCR, culture)



Pitfalls in the interpretation of B.b.-specific antibodies

Delayed antibody-production
(lack of intrathecal antibodies in the first weeks)

Persisting antibodies after recovery / treatment



Therefore:

~~No detection of antibodies = Infection ruled out
Detection of antibodies = Proof of active infection~~

Alternative CSF-markers for LNB?

Elevated in the CSF of LNB patients vs. „control patients“:

- IL- 6 *Weller et al., Arch Neurol 1991*
- GFAP *Dotevall et al., Infection 1996*
- Subset of MMP *Perides et al., J Infect Dis 1998*
- IL-12 and IL-18 *Grusell et al., J Neuroimmunol 2002*
- IL-18, IL-1 β , sIL-1RII *Pietruczuk et al., Neurol Neurochir Pol 2005*
- IL-4 and IFN- γ *Widhe et al., Int Immunol 2005*
- CXCL11 *Rupprecht et al., J Neurol 2005*
- C1q, C3, C3a, C4 *Henningsson et al., J Neuroimmunol 2007*
- ssICAM-1 *Moniuszko et al., Cytokine 2012*

Antigen of *B. burgdorferi* without antibodies in CSF detected

Coyle et al., Neurology 1995

Neopterin (LNB vs. other inflammatory CNS-diseases:

Sensitivity 88.6%, Specificity 65%)

Hytönen et al., J Neuroinflammation 2014



The chemokine CXCL13 (BLC): A putative diagnostic marker for neuroborreliosis

Abstract—Using protein expression profiling, the authors identified an upregulation of the chemokine B lymphocyte chemoattractant (BLC) in the CSF of patients with neuroborreliosis but not in patients with noninflammatory and various other inflammatory neurologic diseases. This upregulation was confirmed by ELISA, showing increased BLC levels in every neuroborreliosis patient while being undetectable in patients with noninflammatory neurologic diseases. These results point to BLC as a putative additional diagnostic marker for neuroborreliosis.

NEUROLOGY 2005;65:448–450

T.A. Rupprecht, MD; H.W. Pfister, MD; B. Angele; S. Kastenbauer, MD;
B. Wilske, MD; and U. Koedel, MD

INFECTIOUS DISEASE

CXCL13 is a potential biomarker for Lyme neuroborreliosis

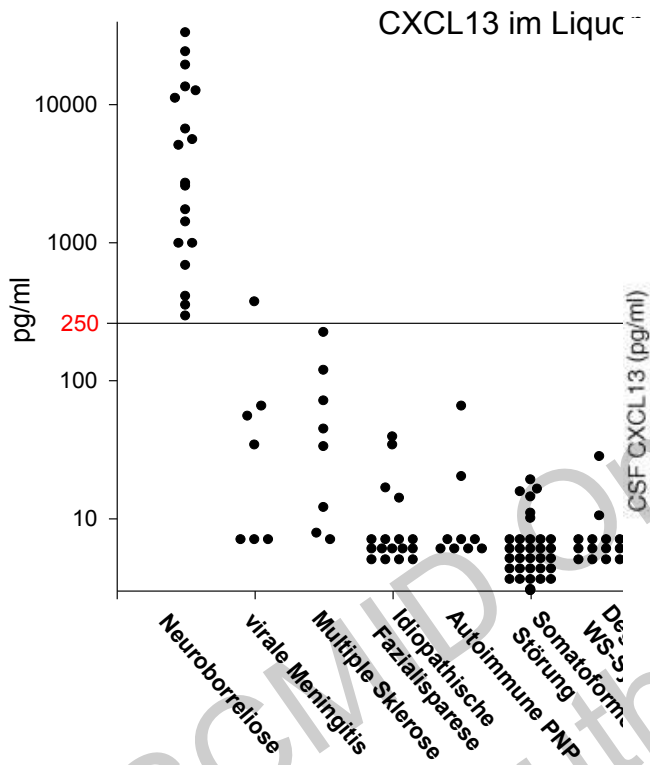
NATURE REVIEWS | NEUROLOGY

Rupprecht et al., Infect Immun 2007

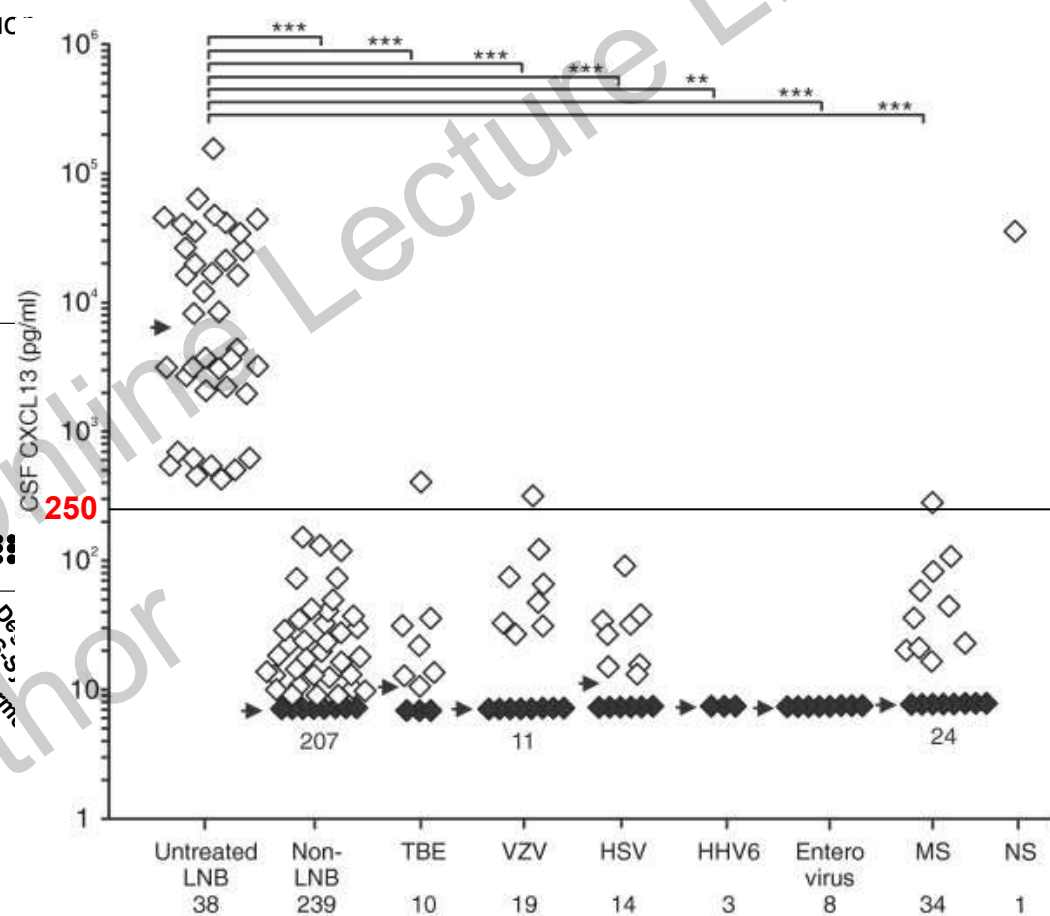
Rupprecht et al., Mol Med 2008

Rupprecht et al., J Neuroinflammation 2009

CXCL13 – recent studies



Rupprecht et al., Nervenarzt 2014

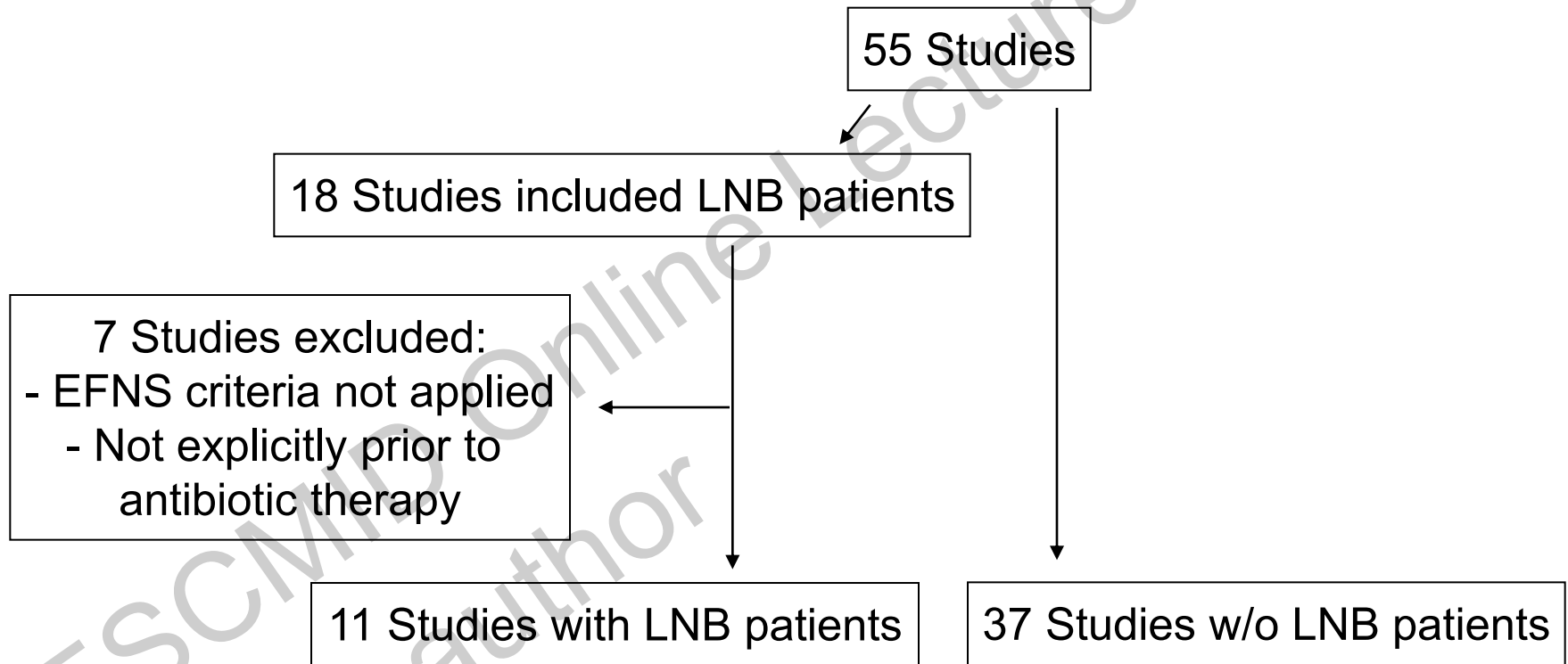


Hytönen et al., JNI 2014

CXCL13 – preliminary results of a meta-analysis



Studies on CXCL13 measurement in the CSF, published in PubMed 2005-2014:



CXCL13 – preliminary results of a meta-analysis

	Disease	n=	cut-off (pg/ml)			
			142	250	500	
Sensitivity	LNB	245	91%	87%	79%	above cut-off
	MS	643	92%	96%	99%	
	CIS	177	96%	99%	100%	
Specificity	Neurosyphilis	30	40%	63%	77%	below cut-off
	Aseptic meningitis	149	94%	97%	99%	
	Bell's palsy	57	95%	98%	100%	
	NIND	813	99%	100%	100%	

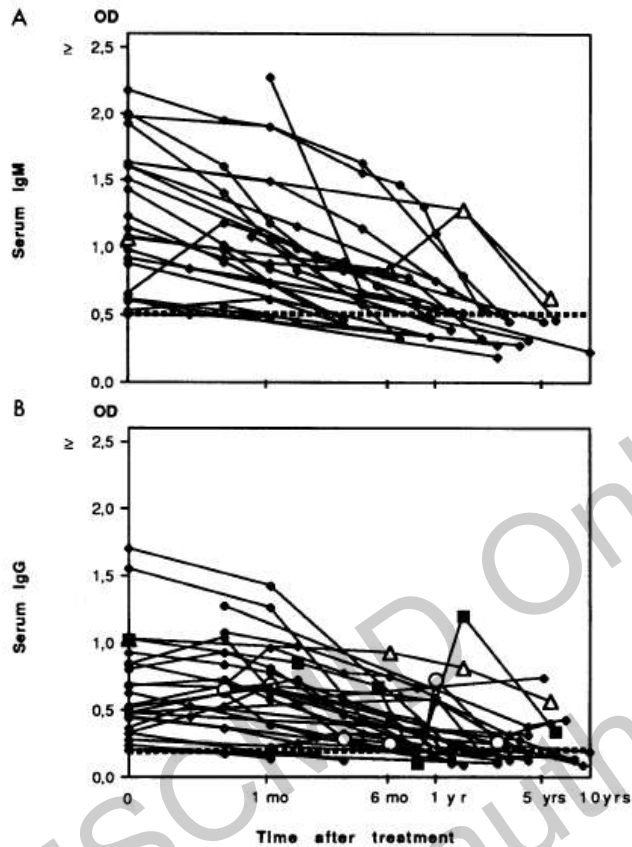
Comparison:

Borrelia-specific CSF/Serum antibody index

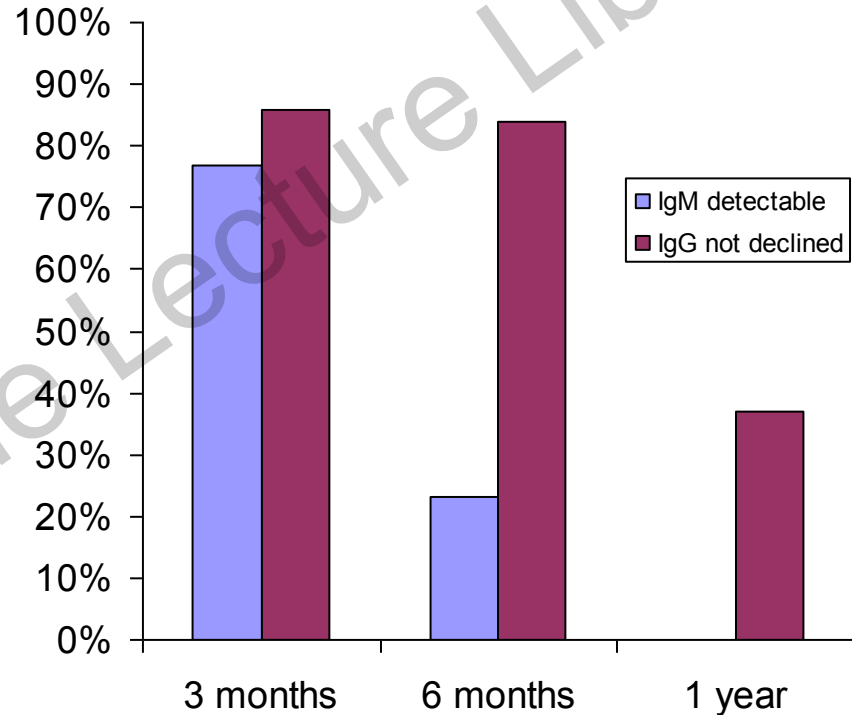
↳ Sensitivity 75-86%, Specificity 96-98%

Tumani et al., Neurology 1995
Ljostad et al., Eur J Neurol 2007
Djukic et al., J Neurol 2011
Schmidt et al., Neurology 2011

Treatment marker: Serology in LNB follow-up



Hammers-Berggren et al., JCM 1994

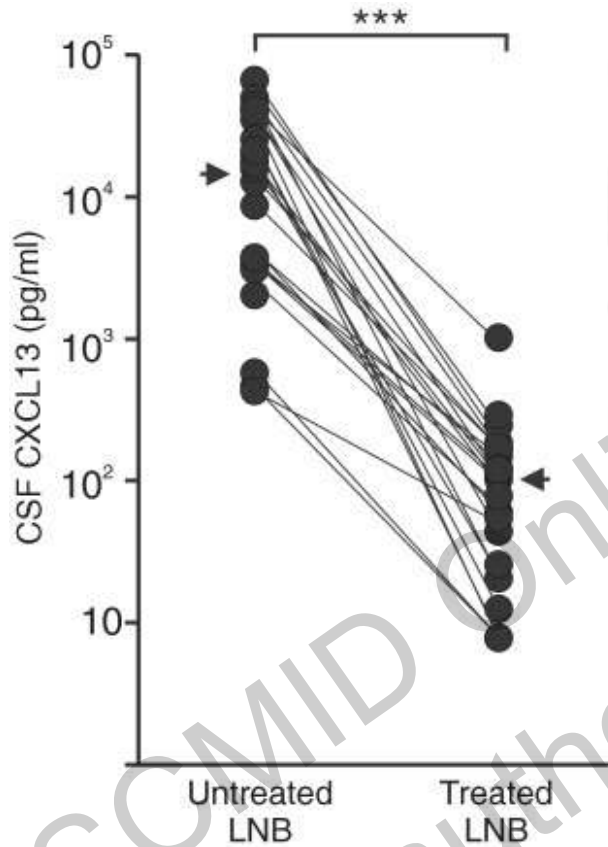


Kaiser et al., Nervenarzt 2004

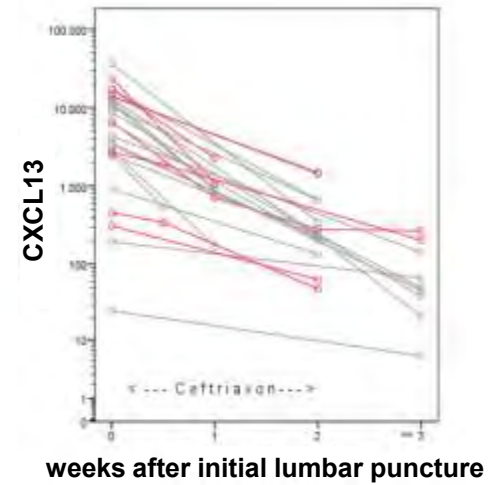
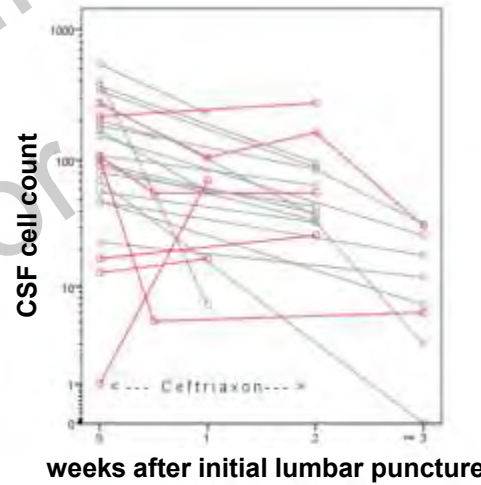
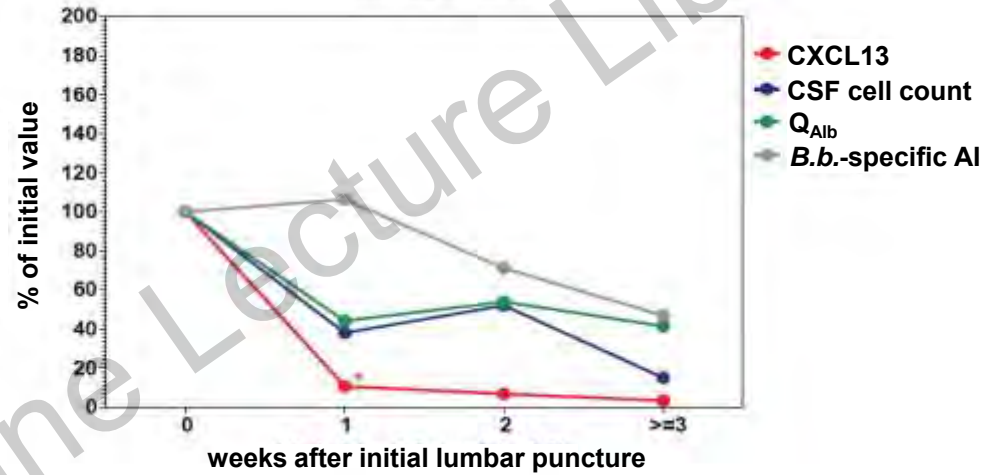
Serum antibody titer correlates not with treatment response

Fleming et al., Eur J Clin Microbiol Infect Dis 2004

Treatment marker: CXCL13



Hytönen et al., JNI 2014



Senel, Rupprecht et al., JNNP 2009

Conclusion & Take-home message



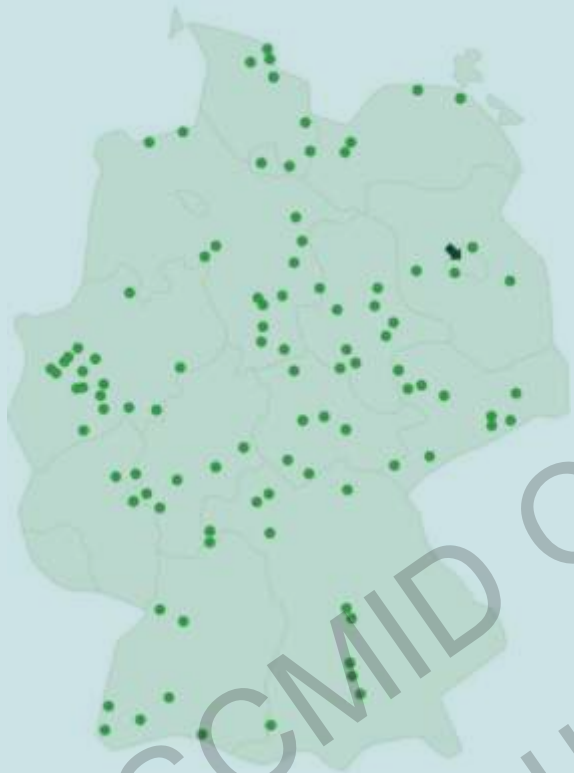
„Gold standard“ for the diagnosis of LNB:

combination of { clinical picture
CSF pleocytosis (EFNS-criteria)
B.b.-specific AI

CXCL13 as additional CSF-marker in

- ✓ Early cases (≤ 2 weeks of disease duration)
- ✓ Unclear cases (differentiation to subsided disease)
- ✓ Treatment marker

Serology alone is **not** sufficient for the diagnosis of LNB



Thank you for listening!

HELIOS Kliniken

www.helios-kliniken.de