Performance of quantitative measurement of the cytokine CXCL13 in CSF from patients with neuroborreliosis and non related diseases.

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Introduction

Neuroborreliosis is the most frequent invasive presentation of Lyme borreliosis. Clinical and biological aspects can be classical as Garin-Boujadoux-Bannwarth syndrom. Serology is a powerful diagnostic tool using the determination of the specific intrathecal antibody synthesis.

Recently CXCL13 has shown to be useful in early neuroborreliosis diagnostic. We present the results obtained with two kits measuring the quantity of CXCL13 in the CSF.

Material et Method

Two hundred and seventeen CSF were tested for quantification of cytokine CXCL13. Sensitivity was tested on 52 samples of neuroborreliosis (NB) patients with specific intrathecal antibodies (SIA). Specificity was tested on 114 CSF from patients presenting a central nervous system disorder with either known pathogens or idiopathic origin as well as from patients with normal values. The other 51 CSF came from suspected neuroborreliosis without SIA. Determination of SIA was made using the IDEIA Lyme Neuroborreliosis test (Oxoid, Switzerland). Human CXCL13/BLC/BCA-1 Quantikine ELISA (R&D System™, Abigdon, UK) was used to test all 217 CSF.

The second kit, CXCL13 ELISA (Euroimmun, Lübeck, Germany) was evaluated on CSF of 20 patients with SIA and 81 non Lyme patients to compare values and specificity.
Among the known infectious etiologies we selected:

- **17 bacterial meningitis (8 *S.pneumoniae*, 4 *N.meningitis*, 2 *S.aureus*, 2 *L.monocytogenes*, 1 *E.coli*)**
- **17 viruses PCR positive in CSF: (12 enterovirus, 3 VZV, 2 HSV)**
- **14 other infection involving neurological disorders: 6 TBE, 5 Syphilis, 1 parainfluenza, 1 HIV, 1 HCV**

Result

Quantikine R & D Kit

Group of patients	At limit of (pg/ml) 0	20	100	500	
NB with SIA	3	5	10	34	52
NB suspicion without SIA	40	2	2	7	51
CSF pathology of unkown etiology	37	3	1	2	43
Known pathogen	28	6	6	0	40
Other non Lyme	29	2	0	0	31
	137	18	19	43	**217**
Sensitivity (N=52)	**100**	**94.2**	**84.6**	**65.4**	
Specificity (N=114)	**0**	**82.5**	**92.1**	**98.2**	

Euroimmun Kit

Group of patients	At limit of (pg/ml) 0	20	100	500	
NB with SIA	1	3	3	13	20
NB suspicion without SIA	4	1	1	1	7
CSF pathology of unkown etiology	10	3	2	2	17
Known pathogen	31	13	6	1	**51**
Other non Lyme	10	3	0	0	13
	56	23	12	17	**108**
Sensitivity (N=20)	**100**	**95.0**	**80.0**	**65.0**	
Specificity (N=81)	**0**	**63.0**	**86.4**	**96.3**	

Discussion

- CXCL13 level **>500 pg/ml is specific** but seems to lack sensitivity
- **SIA is the reference** microbiological test for neuroborreliosis but the correlation with CXCL13 is not very high
- **SIA may persist** for monthes after treatment
- SIA positive (20) showed **antibodies in CSF**
- NB selection needs complete **clinical and biological** data
- Testing CXCL13 on CSF of poorly selected patients is not efficient
- Level >500 pg/ml have not been found with **other** microorganisms
- Non **infectious etiology** may generate level >500 pg/ml (4.6%)

Discordance	Nb.	Discussion
NB SIA+	4	SIA positive for IgG (n=3) and IgM (n=1) only Treatment before lumbar puncture not known 1x low seropositivity in CSF, no other data available 1x seronegative, pleocytosis at 156 M/l, protein=1009 mg/l 1x no clinical biological data available 1x weak IgM SIA, PF, weak pleocytosis at 23 M/l,
Unknown etiology	4	**>500** : high pleocytosis and proteorachia. 1x gammapathy lambda 1x 3 meningitis in 6 months and x CRO treatment ! **<500:** 1x proteorachia (606 mg/l) alone serum IgM+ alone 1x proteorachia (930mg/l) and pleocytosis (47 M/l)
Other than Borrelia	7	3 x *S.pneumoniae* meningitis 3 x VZV PCR positive in CSF 1 x EBV PCR positive in CSF ; Patient HIV and syphilis

Conclusion

The use of CXCL 13 quantification in CSF is not recommended for routine diagnostic procedure. However according to literature these assays can detect early neuroborreliosis before the seroconversion in serum and intrathecal antibody response. Furthermore CXCL13 does rapidly respond to treatment (1)

Référence.
1.CXCL13: a biomarker for acute Lyme neuroborreliosis. Investigation of the predictive value in the clinical routine. T.A. Rupprecht, C. Lechner, H. Tumani, V. Fingerle. (German) Nervenarzt 2014