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The Performance of Multiplex Bead Antibody Index Determination, Flagellar Antibody Index and CSF-CXCL13 in the Diagnostics of Lyme Neuroborreliosis (NB) in a hyperendemic Setting

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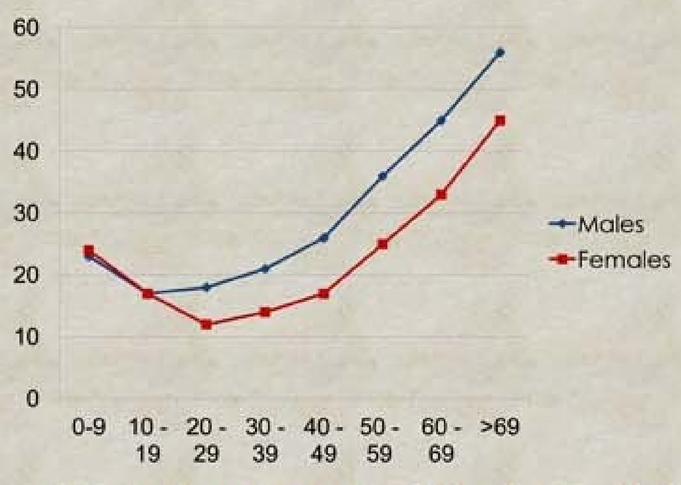
Conclusions

Serum borrelia antibodies are of limited value in diagnosing NB in a high endemicity situation. The rate of intrathecal synthesis of IgG borreliaspecific antibodies (ABI) is also high in the population from a hyperendemic region. Under such circumstances, an indirect marker as ABI is not a reliable indicator of NB. The performance of different methods for assay of ABI is variable as demonstrated by the FN figures.

The chemokine CXCL13 in CSF is a valuable surrogate marker for borrelia induced inflammation, which together with a sensitive ABI, may considerably improve the diagnostic accuracy.



Serum borrelia IgG antibody positivity in patients from the Åland Islands. Age and gender dependent percentual values are calculated from 17 428 samples.

Introduction & Aim

The clinical case definitions for NB in Europe emphasize the CSF/S - ABI as an important disease marker (EFNS GL 2010, Stanek 2010).

The Åland Islands is a hyper-endemic region with estimated annual incidence of LB over 1000 * 10^5. This is reflected in a high seropositivity rate in the population.

In the present study we evaluated the presence of a positive ABI and its diagnostic performance by two methods in a clinical population.

Additionally, we calculated the impact of a complementary determination of CSF-CXCL13 on the overall diagnostic performance in suspected NB (Schmidt 2011).

Materials & Methods

We evaluated 56 cases referred on the suspicion of early cranial nerve or central NB. The clinical picture included the epidemiologic setting with tick exposure, symptoms of meningo-radicular engagement, cranial nerve paresis or unusual fatigue with cognitive dysfunction existing for less than 6 months.

A CSF-leukocyte count > $5*10^6$/l indicated pleocytosis and required for NB. Serum borrelia antibodies were assayed by C6 Lyme ELISA Kit, (Immunetics, USA) and by recomWell/recomBead IgG (Mikrogen, Germany) in a 2-step procedure.

IgG-ABI was assayed by multiplex bead technique, recomBead(Mikrogen, Gerrnany) and by capture ELISA, IDEIA Neuroborreliosis IgM/IgG, (Oxoid,UK). The chemokine CXCL13 in CSF was assayed in a subgroup of 28 by ELISA (R&D, USA).

Thorough differential diagnostic evaluation as well as the results of antibiotic treatment and follow up after 3 months were also taken into account for the final diagnosis.

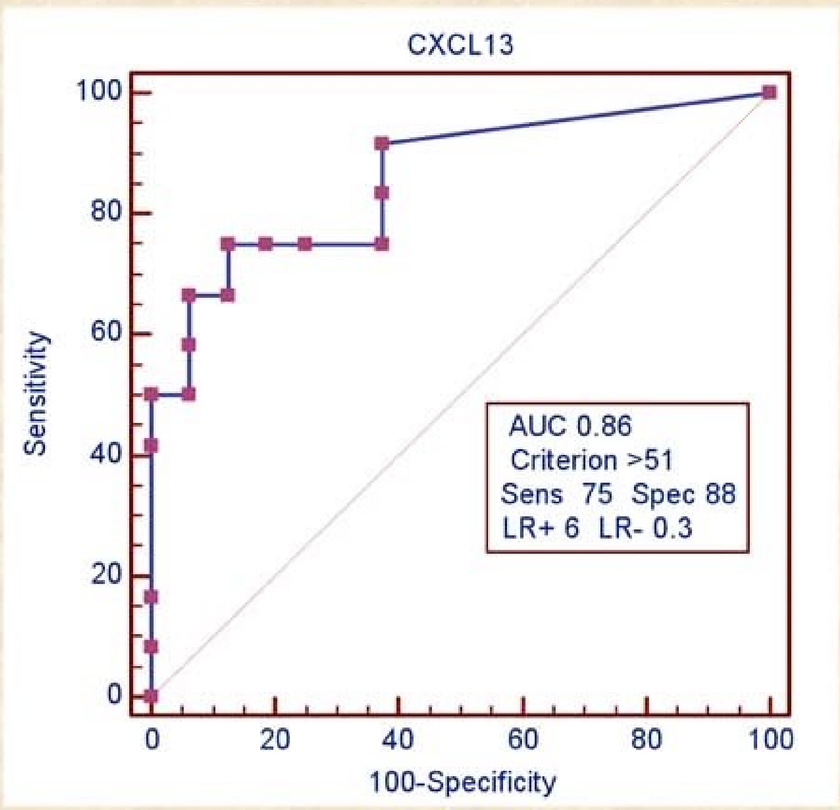
Results

Figures for serum antibodies.

Parameter % (95 % CI)	2 - step IgG	C6 - peptide
Sensitivity (TP)	61 (39 –80)	91 (72 - 99)
Specificity (TN)	61 (42 –77)	49 (31 –67)
False positives (FP)	39 (23 –58)	52 (34– 69)
False negatives (FN)	39 (20 - 62)	9 (1 – 28)
LR+	1.6	1.8
LR-	0.7	0.2

Figures for Csf - ABI

Parameter % (95 % CI)	Multiplex IgG	Capture IgG	Capture IgM	Capture IgG or M
Sens (TP)	91 (72 – 99)	70 (47 – 87)	48 (27 – 69)	74 (52 – 90)
Spec (TN)	52 (34 – 69)	79 (61 – 91)	91 (76 – 98)	73 (55 - 87)
False positive (FP)	49 (31 – 67)	21 (9 – 39)	9 (2 – 24)	27 (13 – 46)
False neg. (FN)	9 (1 - 28)	30 (13 – 53)	52 (31 – 73)	26 (10 – 48)
LR+	1.9	3.3	5.3	2.7
LR-	0.2	0.4	0.6	0.36



Antibody determinations in serum are not of definite diagnostic value, apart from the low FN value for C6 peptide. In Csf the capture ABI tests have very high FN ratios whereas multiplex ABI has a low FN ratio. The assay of CXCL13 adds considerably to the diagnostic accuracy. Combination of pre-test probability with several diagnostic findings is important for optimal diagnostic performance. A pre-test P of 20 % gives a post-test P of 77% for NB when calculated from S-C6, pleocytosis and ABI. Addition of CXCL13 to the calculation gives a post-test P of 95 %, which is clearly above the desicion limit.

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