Author's response to reviews

Title: Cerebrospinal fluid CXCL13 in Lyme neuroborreliosis and asymptomatic HIV infection

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Author's response to reviews: see over
Cover Letter

Second revision of “Cerebrospinal fluid CXCL13 in Lyme neuroborreliosis and asymptomatic HIV infection”

Here follows a point-by-point description of changes made in response to the concerns raised by the reviewers.

Reviewer: Tobias Rupprecht

Reviewer's report:

The authors have addressed some of the points of concern. However, there are still some major points to be addressed before the manuscript is ready for acceptance.

1) The authors state in the discussion section, that the difference between the LNB population in the cross-sectional and the longitudinal study in respect to the CXCL13 levels “might be a random effect”. They should calculate a p-value (comparing the CXCL13 values in both groups) to look for the significance of the difference. I guess, that the p-value is below 0.05 (arguing against a random effect) - this value should be added to the results-section and the interpretation should follow in the discussion section.

A p-value for the difference in CSF CXCL13 levels between the LNB patients in the longitudinal and the cross-sectional study has been calculated in the results section (P = 0.065). The interpretation in the discussion section has been changed and the random-effect cause has been played down. It now reads:

The median CSF CXCL13 values differed between the longitudinal study (3,727 pg/mL) and the cross-sectional study (500 pg/mL), although the difference did not reach statistical significance (P = 0.065). This cause of this difference is not clear. It could be a random effect, or it could related to the difference between the two groups in the CSF levels of mononuclear cells (median 118 cells/µL compared with median 58 cells/µL), as we show a significant correlation between CSF levels of mononuclear cells and CXCL13 in Figure 4B.

2) In figure 3, there are only 18 dots in the LNB group, while in the methods section, they describe 19 patients - where is the missing one?

19 patients with LNB were analyzed in the cross-sectional study. The reason why only 18 dots were seen in figure 3 must have been due to a glitch in the statistics program. There are four patients with CSF CXCL13 values within a small range (496, 498, 500, 500 pg/mL). The plot has been redone and changed according to the points of concern raised under point 3. It is now plotted with 16 dots for 16 LNB patients.
3) In the response to the reviewers, they state that 16 of 19 patients have - according to the criteria of the EFNS - a confirmed LNB. They argued: As this is the majority, they did not further show the exact CXCL13 values of the three patients without confirmed LNB. This is not adequate. As every value is important (it's not about a general significant difference between both populations but about the usefulness of CXCL13 as diagnostic marker!) they should indicate exactly these three CXCL13 values. If they are unusually high or low, they should be definitively omitted. If, for example, all three values are below 250pg/ml, they definitely influence the calculation of sensitivity and specificity of CXCL13 and therefore the conclusion of the manuscript.

The three LNB patients in the cross-sectional study for whom there was no positive AI (1 with a negative AI and 2 where the AI could not be calculated) had CSF CXCL13 values of 22, 46, 102 pg/mL. As all these values were below 250 pg/mL these patients have now been excluded and all related calculations, discussion sections, figures (figure 3-5) and the table have been re-done. There is still a overlap between the LNB and the HIV patients as seen in figure 3 but the interpretation has been modified and it is now called a "clear overlap" instead of a "considerable overlap".

**Reviewer 2: Kenneth Tyler**

- Nu further changes required.

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Sincerely,

Daniel Bremell  
Niklas Mattsson  
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Carsten Wikkelso  
Henrik Zetterberg  
Lars Hagberg