Author’s response to reviews

Title: The NeBoP score - a Clinical Prediction Test for Evaluation of Children with Lyme Neuroborreliosis in Europe

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Response to reviewers on the manuscript

“The NeBoP score – a Clinical Prediction Test for Children with Lyme Neuroborreliosis in Europe”.

To the Editor:

We are very grateful for valuable comments on our research and we do believe reviewer’s comments have helped us to improve our manuscript. We are aware of weaknesses in the study, which are commented on by reviewers, and we hope our response to reviewers and corrections in the manuscript are satisfactory and will fulfil requirements for publishing.

The STARD checklist is fulfilled concerning important issues on diagnostic accuracy including the representativity of the patient sample, pre-test validation of the test and precision of the test. However, since our study validates a predictive test, not a strict diagnostic test, the issue of name of registration or registration number is not relevant for our study.

To reviewers:

Reviewer 1: "One concern ... is the small sample and clinical heterogeneity of the negative control subjects”.

Response: Admittedly, the sample size of negative controls could have been larger than 49, this is weakness of the study. However, it was the sample size we could achieve during the time period of the study in our clinical setting (added in Discussion row 259-262) and the median age and sex distribution did not differ between controls and LNB patients, which is a strength of the study. True, among 49 negative controls there were many different medical illnesses with large clinical heterogeneity. However, when evaluating a predictive test it is of importance to add controls without clinical similarity to patients (in this study 49 negative controls) as well as controls with clinical similarity to LNB patients from a clinical relevant setting (in this study 107 Non-LNB patients). We have added these two control groups in our study and we believe the heterogeneity of controls with other diagnosis therefore can be acceptable. Negative controls without any symptoms (i.e. healthy controls) could not be included in the study due to the fact that a lumbar puncture cannot be performed on healthy children out of ethical reasons (added in Discussion row 247-256 in the manuscript).

Reviewer 1: “A more useful comparison would be 49 subjects with enteroviral meningitis”.

Response: Concerning controls with enteroviral infection, a few such patients are included among controls in our study (n=7), but they could admittedly have been higher in number. Patients with enteroviral infection differ from LNB patients in clinical manifestations and laboratory data, clearly shown in previous studies (Shah 2005, Tuerlinx 2003, Eppes 1999). Furthermore, there are some patients with viral meningitis
of unknown aetiology (unfortunately not tested for enteroviral PCR in CSF, n=6) among controls and these patients are also valuable from a relevant clinical setting. Thus, we find it acceptable with the amount of enteroviral controls in our study, but we have added a comment in discussion (row 257-258).

**Reviewer 1:** “Another important comparison would be with patients who had suppurative bacterial meningitis”... “Would the NeBoP score adequately differentiate Lyme from pneumococcus or meningococcus?”

**Response:** Suppurative bacterial meningitis is mentioned as an important diagnosis for comparison and the question is raised whether the NeBoP test could differentiate Lyme from pneumococcus och meningococcus? Admittedly, it would have been of interest to include such a control group and this is added as a weakness of the study in the discussion part of the manuscript (row 257-258). However, the symptoms and the CRP level clearly differ between LNB and bacterial meningitis, so in clinical paediatric practise, this would probably not be an important issue. Patients with bacterial meningitis will receive antibiotic treatment on clinical picture and CRP whereas patients being evaluated for LNB will receive antibiotic treatment if they have 3 points or more in the NeBoP score. Importantly, patients with 2 points or less in NeBoP score will NOT receive antibiotic treatment, which is one of the useful findings in this study.

Reviewer 2:
No further comments, reviewer 2 is pleased with the manuscript.

Best regards
Barbro H Skogman, corresponding author