Author’s response to reviews

Title: Cerebrospinal fluid pleocytosis level as a diagnostic predictor? A cross-sectional study.

Authors:

Anne Marie Ahrens (Anne.Marie.Ahrens@rsyd.dk)

Thomas Sydenham (Thomas.Sydenham@dadlnet.dk)

Mads Nybo (Mads.Nybo@rsyd.dk)

Aase Bengaard Andersen (Aase.Bengaard.Andersen@regionh.dk)

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Author’s response to reviews:

Dear Sir,

Thank you very much for the very useful comments provided by the two reviewers. We have addressed all comments and revised the manuscript as stated below. We hope our improved manuscript will be worth considering for publication. We have written our point-by-point replies in the text using colored text font.

During the time of the review the first author got married and changed name from Anne Marie Ahrens to Anne Ahrens Østergaard and the name of the author (and e-mail) has therefore changed.

Editor Comments:

1) Please separate Results and Discussion into two distinct sections. This has been done

2) Please move the list of abbreviation out of the Declarations section to after the Conclusions. This has been done

4) Please remove the titles/captions included in figures 1, 2 and 3 and place them at the end of the main manuscript, after the References, in a section ‘Figures’ where you list the following information: * Title of data (e.g. Figure 1) and * Description of data. For more information on this, please go to https://bmcclinopathol.biomedcentral.com/submission-guidelines/preparing-your-manuscript#preparing+figures
We have removed the titles of figure 1 – 3 and placed them at the end of the manuscript as required.

5) Please confirm that you have permission to use the data from the database for this study and include a statement to that effect in your manuscript. Anonymized datasets can be available upon request, and this is now specified in the manuscript.

Reviewer reports:

Reviewer #1:

Cerebrospinal fluid pleocytosis level as a diagnostic predictor? A cross-sectional study.

This is an important area of research that is relevant to everyday Neurology practice. However, this paper requires major revisions before publication and additional statistical review.

Comments:

1. Line 46. Better specified as 'non-infectious neurological diseases'. We agree and we are now using this term.

2. The 'Conclusions' in the abstract are more than what is shown in the 'Results'. The conclusions need to be aligned with the results. Thank you for your comment. This has been corrected.

3. It would be good to define the term 'CSF pleocytosis' in the section of Background. This has been included.

4. Line 86: it should be stated '1 leucocyte per 1000 erythrocytes'. Not vice versa. Thank you, this has been corrected.

5. Line 94: Is it 'culture' or 'cultivation'? We have chosen to specify this as microbiological analyses as it also includes PCR, sequencing, antibody and antigen testing.

6. Line 101, items 4) and 5): The justifications in these two items to classify them as CNS infection are not strong enough. 4) If the patient was only 'observed for possible infection' but this was not included in the final diagnosis, it is likely that the clinician did not feel confident that it was indeed a CNS infection. 5) The mere empirical treatment with antibiotics does not justify a diagnosis of CNS infection if the clinician did not feel that it should be included in the final diagnosis. Thank you for considering this. We feel item 4 is
strong as we refer to other Danish studies that have shown that discharge diagnosis are not always very well related to what the patient was hospitalized for (Gradel 2015, Henriksen 2014). In some cases, the lumbar puncture was very little part of why the patient was hospitalized. Therefore, it has been necessary to review all charts. According to item 5 we concluded for this study that if the clinician suspect CNS infection enough to give full treatment for CNS infection and no other cause of pleocytosis was found it is fair to categorize this as the final diagnosis. We hope, the reviewer will agree with us on these aspects.

7. In order for the reader to make sense of the results, the use and interpretation of the Charlson score needs to be described under statistical analysis. Thank you for noticing this. It has been included.

8. CNS infection is also a neurological disease. Hence, the current categorisation as 'CNS infection' and 'Neurological' as separate categories is confusing. If at all it should be categorises as 'non-infectious neurological disorders'. We agree with the reviewer. ‘Neurological’ have been changed to ‘non-infectious neurological disease’

9. There are errors in the labelling in the table. This has been corrected.

10. A major limitation in this study is that no attempt has been made to differentiate between the different types of infections which would have an enormous impact on CSF pleocytosis. Categorising bacterial infections which have high pleocytosis with viral which have low pleocytosis diminishes the significance and usefulness of this study. Furthermore, infections such as tuberculosis and fungi would present a completely different CSF profile and if these are not teased out, these results diminish in significance. In the study we wished to show the differential diagnoses to pleocytosis. Many others have showed the difference of viral and bacterial meningitis as we refer to in the background section. As appendix shows no patients was found to suffer from CNS infection due to fungi or tuberculosis. This might due to only hospitalized patients were included and many patients have performed diagnostic lumbar puncture as outpatients as shown in Figure 1.

11. Data regarding aetiological diagnosis such as microscopy, culture, antigen tests, PCR which are gold standards for the diagnosis are lacking. The category of 'CNS infection' needs to be corroborated by such data. We agree that it would have been better if all patients had an aetiological diagnosis made. However in some cases an aetiological diagnosis is not found. This might due to prior antimicrobial treatment or improved methods since the study was performed. This has been included in limitations.
12. CSF:serum glucose ratio which is relied upon heavily in clinical practice in differentiating the different aetiologies of CSF pleocytosis has been completely left out of this study. It needs to be included if these data are to be externally valid. Data for 141/262 patients has been included.

13. The discussion does not highlight what this study has added to what is already known with regard to CSF pleocytosis. Most of what has been presented is already known. It may be true that the conclusions of this paper support what is considered common knowledge. However, we have not found any newer literature on this topic and it is an issue we very often discuss in our daily clinical work: if you do a lumbar puncture and find X cells/microliter- what are the most likely differential diagnoses?

14. Would it be statistically possible to define a cut-off level for pleocytosis, along with positive and negative predictive values, that would predict CNS infection. We doubt that we can define a cutoff value that would be of any use in real life based on our data. Data on clinical presentation and the time factor (time from symptoms to lumbar puncture) should have been addressed.

Reviewer #2:

This manuscript has excellent qualities to it. It fits a need, which is to correlate the CSF findings of patients with their ultimate diagnosis. The methodology is well described and Figure 1 is highly appreciated.

The major issue with the manuscript is how they identify the diagnosis. It appears that many things are lumped into "CNS infection" without clear defined organisms. This is problematic because then it is not clear how well their conclusions reflect "truth". I would recommend that they define CNS infection in the following manner:

1. Definite- organism grown or identified by PCR 2. Probable- paraclinical data/response to antibiotics 3. Possible (suspected)- none of the above, but written in discharge diagnosis

I would use such definitions for encephalitis/myelitis as well.

Very good point. The reason that we did not do this is that the groups would have become very small. We have included results for how many of the diagnoses that were paraclinically confirmed.
Smaller issues:

1. Table II- malignancy column, under % it says "7375". This makes no sense (% w/ < 10 WBCs) Thank you for noticing, this have been corrected.

2. Appendix: "other" needs to be specified for each category. For example- under "Neurologic causes" 25% of the cases are "other" and the mean CSF leukocyte count is >100. It would be useful to know what those "other" diagnoses were. We appreciate your comment. All discharge diagnoses in the “other” categories have been included in the appendix.

3. Appendix: the 4 cases of pleocytosis in cancer with "cancer foci elsewhere" have CSF pleocytosis mean of 500!!! This seems unlikely. How would cancer elsewhere cause a CSF pleocytosis. Thank you for your comment. One patient suffered from neutropenic fever during chemotherapy and had 1980 cells/µl. The patient was not found to suffer from CNS infection. This information is now included in the article.

Sincerely,

Anne Ahrens Østergaard; Thomas Vognbjerg Sydenham; Mads Nybo, and Åse Bengård Andersen