Author's response to reviews

Title: Brain Ventricular Dimensions and Relationship to Outcome in Adult Patients with Bacterial Meningitis.

Authors:

Janni L. Sporrborn MD (janni.l.sporrborn@gmail.com)
Gertrud B. Knudsen MD (gertrud_bk@hotmail.com)
Mette Sølling MD (mettesolling@hotmail.com)
Karina Seierøe MD (kseieroe@gmail.com)
Annette Farre (annette.farre@hvh.regionh.dk)
Bjarne Ø. Lindhardt DMSc. (bjarne.oerskov.lindhardt.01@regionh.dk)
Thomas Benfield DMSc. (tlb@dadlnet.dk)
Christian T. Brandt DMSc. (dr.cbrandt@gmail.com)

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Author's response to reviews: see over
Concerning review of manuscript no. 1028084468147711

To the editor

Thank you for allowing us to respond to reviewer comments and further improve the manuscript according to reviewer guidelines.

We have addressed reviewer comments in order of appearance.

Referee 1

Major Compulsory Revisions

1. Data analysis should be restricted to the 81 patients with immediate CT scan. Alternatively, the authors should clearly separate any other group from this one (in the text, the tables and figures), and explain thoroughly why different groups must be used.

Author response: We agree that with the reviewer and as suggested we have rearranged the results section in order to clarify that the primary group of interest is the 81 patients receiving a CT scan in relationship to the diagnostic lumbar puncture. This is the group shown in fig. 1, table 1 and the group employed in our multivariate regression analysis. We have considered if data from the remaining 69 patients could be omitted but we believe that inclusion of this group is necessary to define our meningitis population as well as to elucidate relationships and differences between patients based on the time for imaging and thus the ability to perform data comparisons.

Page 8, line 15-23
Page 9, line 1-6, line 10-13 and line 20-21.
Page 10, line 1 and line 9-10

2. Co-morbidities must be tested for significant effects, in particular for effects on VBR. If an effect of co-morbidity cannot be excluded, omit those patients.

Author response: We agree with the reviewer that co-morbidity could influence our results. We found that our pre-defined immunosuppressive co-morbidities were non-significantly different between survivors and non-survivors among the 81 patients included in the multivariate analysis. Actually, the level of co-morbidity was slightly higher among survivors than non-survivors (42% versus 27%) further minimizing the risk that this could have affected our study conclusions.

We therefore believe that these patients should remain in the study analysis due to reasons given above and due to the fact that, immunosuppressive co-morbidity is a primary risk factor in acquiring bacterial meningitis why omitting these patients could create and alternate study bias. Furthermore, patients with co-morbidity were not excluded from the control group in order to secure the comparability between these populations.

We agree that investigation of our hypothesis could be supported if performed among a population with much lower complicating co-morbidity. However, such a population may be difficult to assemble.

Table 1 – a correction has been made in table 1 where 1 patient among non-survivors had diabetes and not 0 as originally stated. We apologize for this mistake.
3. Patient group and control group was divided into different age ranges. Same ranges should be used for both cohorts.

**Author response:** The authors apologize for this confusion. As suggested we have clarified that both control patients and meningitis patients were divided into the same age groups.

_Page 7, line 4-6_

4. The authors have determined the VBR from several consecutive 2D imaging slices. The strength of this study is that 3D imaging data are available. The authors should perform a full 3D volumetry of brains and ventricles, which could be done with a minor effort of additional work. These results would add a valuable piece of new methodological data to the study and substantially strengthen the manuscript.

**Author response:** We agree that full scale volumetrics and comparison of these results could be of interest illustrating if ventricle expansion varies in the horizontal and vertical planes. The methodology used in the present paper has previously been documented to correlate indeed very well to ventricle volume and to be a methodology superior to simple measures as Evans ratio or bi-caudate index (see references below).

We have experimentally (manuscript refs. 1 and 2), measured ventricle size using both planimetric methods and automated volume estimation. The latter did not improve accuracy, but was, as also pointed to by the reviewer, more work efficient.

It was of significant importance to us that the presented methods could be used in a clinical setting. This is even more important now we are aware that the imaging sessions from these patients could need further attention.

Despite the flaws pointed to by the reviewer, our measure is much more refined than the methodologies used in previous papers in this field (manuscript refs. 3 and 26). Our image material is retrospective and performed for clinical reasons. No further imaging data allowing us to view the full spiral sequence and thus volumetrics, is available.


5. The authors consider too large and too small (pathological) VBR. The patient numbers for too small VBR seem to be low. What would be the explanation of a too small VBR. Is this not a completely different pathology than too large VBR?

**Author response:** We agree with these comments. Our conservative calculations of a pathological ventricle size may be to crude to actually identify the true number of patients with compressed ventricles due to vasogenic brain oedema. CT is not ideally suited to verify brain oedema other than longstanding or massive vasogenic brain oedema. Thus, CT imaging cannot rule out indices of raised intracranial pressure (ICP) in all cases.

As suggested by the reviewer, the pathophysiology leading to compressed or enlarged ventricles may actually differ whereas the result seem to be the same – raised ICP and reduced perfusion pressure. The clinical symptom for both entities is reduced consciousness.

This issue is commented in the _discussion_ section of the manuscript.

_Page 12, line 14-19._
If we are allowed to speculate further we believe that both conditions may occur in patients dependent on the stage of disease. A vasogenic brain oedema due to opening of the blood-brain-barrier should be present in all patients supported by the general increased CSF protein. The importance of CFS outflow resistance is less well characterized in humans but would increase the amount of CSF leading to a counter-pressure to the increasing brain volume. The balance between these two events is unknown, but a subsequent reduction in blood-volume due to decreased brain perfusion could allow for ventricles to expand and reduce vascular leakage to brain tissue. The development of fulminant hydrocephalus could be the ultimate result as also indicated by others who have used this parameter as a clinical endpoint associated with very poor outcome. This is to our knowledge among the few papers actually presenting data on this issue why we also believe that these original data would be of value to colleagues working clinically with these patients. This may be an essential parameter in meningitis that must be subject to further studies.

6. page 9, last sentence is very confusing. What is the conclusion from these data?
Author response: As suggested we have clarified that data analysis based on the term “pathological VBR” was performed among all patients but also excluding patients with age >70 years due to the increasing variation in VBR among these patients. We believe that this approach is supported by the referenced articles (manuscript ref. 16).
Page 9, line 20-21
Page 10, line 1.

7. page 11, line 12-16: Do not discuss individual patients.
Author response: As suggested, these inappropriate individual patient comments have been omitted from the manuscript.

8. Figure 1b: at least three pairs of images for each age range should be shown
Author response: This is definitely a possibility. If all images are made available as supplemental material this may not be necessary. The primary purpose of the figure is to illustrate that differences between a normal patient and 2 SD in ventricle size may not present as vastly as the difference to frank hydrocephalus. Due to the limited space, we would prefer to use the required additional space for the included tables if this request is considered acceptable to the referee and editors.

Discretionary Revisions
1. If possible with the number of patients, an assessment of the effect of pathogen type would be extremely interesting.
Author response: We agree that the suggested analysis would be of significant interest for the assessment of risk factors and pathogen involvement in brain pathology. We believe that the limited no. of patient and non-significant differences in distribution of pathogens between different outcomes does not allow for any further analysis.

2. The paper might greatly benefit from additional Figures illustrating the large amount of data shown in Table 1-3.
Author response: We agree that the tables contain many data. We do believe that demographic data as presented in table 1 should remain so as to adhere with standard
presentations of patient data in comparable studies. The no. of results presented in the data-tables 2 and 3 are difficult to contain in a figures. The results from table 3 could be limited to a presentation in the results section if considered advisable.

3. The authors should show one slice of each patient (for all patients) in a supplementary Figure

Author response: As suggested by the reviewer, a supplementary figure containing an image for each patient can be made available upon publication.

Minor essential Revisions:
1. page 6, line 7/8: indicate how many patients per age range were used
2. page 12, line 18: where
3. page 13, line 13: Fourty
4. Figure 1a: indicate VBR 0.8 and 0.12 by horizontal lines in the plot

Author response: All minor revisions have been corrected and updated according to reviewer comments.
(Page 8, line 13-14).

Referee 2

Minor essentials

Measurement of ventricle size

More information is required to understand the method used to obtain the measurements of the ventricle area...where is the boundary drawn for the cortex ie around the pia surface .this is crucial to the paper and this should be described in more detail

Author response: As suggested we have clarified that the brain cortex ROI was drawn lining the pia mater. A supplementary image displaying the method has been added as a supplemental file.

Page 6, line 15-16
Supplementary file 1.

What is the reason for the increased mortality with increasing CSF protein level due to bacteria in CSF neutrophils etc. is this contributing to CSF obstruction due to choroid plexus injury .Need to expand this in the discussion (page 13 20-22)

Author response: As suggested we have corrected the theory of CSF protein impact on survival. In bacterial meningitis, CSF protein is considered an indicator of BBB permeability and has previously been shown to be a risk factor for poor outcome from bacterial meningitis (supplemental references see below). In studies of hydrocephalus pathophysiology, increased CSF protein is suggested to increase CSF viscosity and the risk of developing hydrocephalus. This has however not been substantially documented.

Page 11, line 12-17

Is the VBR a reversible radiological index for example in survivors? does this return to within normal limits or is this a longstanding radiological feature. Would be of interest to have a longstanding follow up of this study.

Author response: The authors believe that the VBR would be reversible since brain ventricles must comprise a plastic system. We were eager to document ventricle plasticity, but routine imaging in patients recovering from meningitis was of course not performed. We agree with the suggestions that a study performing CT imaging after discharge would provide essential documentation for the impact of ventricle enlargement if size was normalized in patients surviving to discharge and with good outcome.

Perhaps a sentence about the clinical importance of the VBR.... did this data influence clinical management

Author response: As suggested we have added a sentence concerning potential clinical importance and strategies.

Since our data were collected retrospectively our measure of VBR did not influence patient treatment.

Please also see answer below to referee 3.

Page 12, line 14-19 and page 15, line 3-6

p12 18 change text too crude, where, very low clinical scores
p14 line 2 number not no.
p14 line 6 At last not sure what this refers to
p4 line 11 ventricle size other than

Author response: Errors on page 12 and 14 have been corrected.

Referee 3
The manuscript investigates the prognostic value of enlarged brain ventricles in bacterial meningitis. The whole work is well done. The data are relevant and seem reliable.

Additional discussion should be added about the hypothetical cause of the ventricular enlargement: it can be acquired due to the meningitis but also to preexisting comorbidities (alcohol abuse for instance). This can be a serious bias in the interpretation of the data although not modifying the prognostic value of the VBR index. If in fact the VPR is acutely increased in the context of meningitis, repeated subtractive spinal tap or external CSF derivation could be proposed as a therapeutic approach early in the course of the disease.

Author response: These suggestions seem indeed very interesting since the method using repeated lumbar puncture to drain CSF was the main methodology used by Glimåker et al. who did recently publish a study showing that controlling the intracranial pressure did improve survival from bacterial meningitis (the study unfortunately used a historical control group which may have affected study conclusions)
Repeated draining of CSF is also used in patients with cryptococcal meningitis. These patients also suffer from ventricle enlargement and the draining relives their headache and confusion.
Repeated CSF draining may very well be the treatment of choice.
Page 12, line 14-19 and page 15, line 3-6
Finally the clinical relevance of the method has to be questioned because not feasible in the routine practice. Further work should be prospective, with serial brain CT imaging, and proposal of a surrogate ventricular enlargement measure well correlated to the VBR.

**Author response:** The authors agree with the ideas suggested by the reviewer. As also replied to referee 2, we had hoped that imaging sequences of patients later in the course of disease could be available. But of course repeated imaging was only used in patients not responding adequately to treatment and with very much timely variation. A CT scan performed after clinical recovery is essential to evaluate the recovery from supposed ventricle enlargement.

We believe that our data do suggest a more rigorous approach towards evaluation of brain imaging and that brain imaging should be mandatory for these patients upon admission. The approach can be used in the clinical routine, but we agree that the (so far) wide borders of normal ventricle size could make this difficult. However, in combination with the clinical evaluation this may be possible.