**Author’s response to reviews**

**Title:** Value of CT and three-dimensional reconstruction revealing specific radiological signs for screening causative high jugular bulb in patients with Menière's disease

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**Author’s response to reviews:**

Dear Reviewer:

Thank you for your comments concerning our manuscript entitled “Value of CT and three-dimensional reconstruction revealing specific radiological signs for screening causative high jugular bulb in patients with Menière’s disease”. Those comments are all valuable and very helpful for revising and improving our paper. We have studied comments carefully and have made correction which we hope meet with approval.

Technical Comments:

Editor Comments:

We operate a transparent peer review process for this journal where reviewer reports are published with the article but the reviewers are not named (unless they opt in to include their name).

Reviewer reports:

Reviewer 1:
General
1. 'Menière' is spelled differently throughout the article (Menière/Ménière/Meniere).
   Response: Thank you for your suggestion. We have corrected it. Meniere’s is spelled throughout the article.

Background
3. In the first paragraph, it is stated that EH may be caused by deficient absorption in the sac (ES) or obstruction of the endolymphatic duct (ED). Thereafter, the vestibular aqueduct (VA) is mentioned but without explaining the anatomical position of the ES and ES in reference to the VA. It would be helpful for readers, especially if they are not familiar with the anatomy of the inner ear, to be informed about their anatomical relationships.
   Response: Thank you for your suggestion. We have corrected it. Page 4, line 76-77, vestibular aqueduct (VA), which contains the endolymphatic duct and the infratemporal endolymphatic sac, resulting in endolymphatic hydrops and Ménière-like symptoms.

4. The authors write "although numerous radiological studies have shown smaller VA dimensions and high rate of JB abnormalities among affected individuals, suggesting that HJB is likely to interfere with VA, causing endolymphatic sac dysfunction and the development of EH". The word although indicates a contradiction in the following sentence, but no contradictory finding is presented. Please clarify.
   Response: Thank you for your suggestion. We have corrected it. Page 4, line 82-83, ‘However, with the exception of certain case reports, which surgically demonstrated that HJB could obstruct the VA, most studies only identified a nonspecific radiological sign, such as JB-related VA dehiscence and JB diverticulum’

5. "most studies only identified a nonspecific radiological sign that did not hold great potential for providing a clinically meaningful understanding of the association between the VA and HJB”. Which nonspecific radiological signs is this in reference to? Why did these signs fall short?
   Response: Thank you for your question. As the nonspecific radiological signs, such as smaller VA dimensions, JB-related VA dehiscence and JB diverticulum, could be detected not only in patients with MD but also in the normal population, the identification of these radiological signs did not hold great potential for providing a clinically meaningful understanding of the association between the VA and HJB.

6. "the lack of consensus over the description of HJB and its definition is a problem that has resulted in the existence of different interpretations of HJB”. Is the lack of consensus due to the use of different reference levels above which the jugular bulb if defined as high riding? If so, or in case of alternative reasons, consider providing some examples of different definitions for HJB in existing literature and/or provide a more general explanation for the variable definition of HJB. Why do different definitions exist in current literature?
   Response: Thank you for your question. Yes, the different reference levels above which the jugular bulb was defined as high riding were used in literature. We have written some examples of different definitions for HJB in existing literature. The reason for different definitions exists in current literature is unclear.
7. Following question 5: in the last paragraph, it is described that no consensus classification system for JB morphology exists. Could you elaborate on the decision to use the classification system of JB proposed by Manjila and Samaan? The rationale to use this particular classification system does not become clear throughout the article.
Response: Thank you for your question. The rationale to use this particular classification system has been explained in the discussion in page 12, lines 320-326, “as the VA is located between the common crus and PSCC, the current proposal of the Manjila and Semaan classification for JB accounts for the relationship of PSCC; therefore, it is reasonable to postulate that an upward extension of JB above the inferior margin of the PSCC is likely to erode the region of the VA, which could be shown as VA absence (non-visible type) in a Pöschl plane image”.

8. “explore the potential of a specific radiological sign for screening causative HJB”. Please describe which specific radiological sign you aim to investigate.
Response: Thank you for your question. We have written the specific radiological sign in page 5, line 101, “the absence or obstruction of VA caused by HJB”.

Materials and methods
9. For completeness, please state if the clinical diagnosis was evaluated by an otolaryngologist.
Response: Thank you for your suggestion. We had corrected it.

10. 91 patients with a clinical diagnosis of definite or probable MD were referred for hydrops MRI. What is the referral pattern in your institution? Were these consecutive patients (do all suspected MD patients in your institution undergo MRI)? Was CT performed as part of regular care, or solely for scientific research? What was the time delay (range) between MRI and CT?
Response: Thank you for your suggestion. In our institution, only the MD patients with a failure of systematic medical treatment and psychological management (intractable MD) were referred for hydrops MRI. CT scan was performed to detect the ear pathologies, such as inflammatory otitis media, temporal bone neoplasm or trauma, congenital ear anomalies during the same time period. However, 4 patients were excluded due to patients aged <18 years (n=2) or with a history of inflammatory otitis media (n=1) or previous otologic surgery (n=1). A total of ninety-five patients with the clinical diagnosis of intractable definite and probable MD were referred for hydrops MRI in revised manuscript.

11. In the first paragraph, exclusion criteria are described. How many subjects were excluded?
Response: Thank you for your suggestion. We had written the number of subjects who were excluded.

12. For the MRI protocol: why was contrast media administered both intravenously and intratympanic ally? Other authors using delayed Gd-enhanced MRI for hydrops evaluation use a singular route of contrast administration.
Response: Thank you for your question. High-quality imaging in vivo visualization of hydrops with Gd-MRI is very important. Although promising results have been reported using IV-Gd, which has the advantage of not being an off-label use of Gd. Yet, they were too complicate and time-consuming to use for routine diagnostic procedures by the heavily T2-weighted 3D FLAIR sequence. In the present study, the use of IT-Gd and IV-Gd MRI not only improved the
effectiveness of imaging and evaluation techniques for EH, but also prevented the failure of IT-Gd imaging for ~10% of cases, which would have been caused by an insufficient Gd concentration with anatomic barriers to the round window, such as adhesions, bone dust blockage or thickened round window, when the IT-Gd method alone was used.

13. Why were two hydrops sequences (3D-FLAIR and 3D-real IR) obtained in each subject as one would seem sufficient to evaluate the membranous labyrinth? In addition, please provide parameters for the sequences used.

Response: Thank you for your question. Although two hydrops sequences (3D-FLAIR and 3D-real IR) obtained in our institution, in order to uniformly evaluate the membranous labyrinth, only 3D-real IR was used to evaluate hydrops in the revised manuscript and the parameters for this sequence was provided.

14. The paragraph titled 'Gd-MRI' mentions that the degree of EH in the vestibule was assessed visually. This statement seems incorrect as further on it reads that quantitative measures were used to calculate the endolymphatic volume in the vestibule. Did you use the grading method by Wesseler et al?

Response: Thank you for your question. The description “the degree of EH in the vestibule was assessed visually” was incorrect. We have corrected it, “The degree of EH in the cochlea was assessed by visual”. An EH of the vestibule was determinate by the volume-ratio of endolymphatic space to the total vestibule (endolymph to vestibule-volume ratio). According to that described by Wesseler et al (17), this ratio was not estimated based on one section plane alone, but was measured separately in every plane showing the vestibule, and then using the average of those values calculated as the overall result.

15. Regarding CT analysis: the anatomical relationship between the VA and JB was classified into three types. Is this a novel classification system, or has it previously been used in other studies?

Response: Thank you for your question. In order to better understand the alterations of the VA morphology related to HJB in MD, we proposed a novel classification system for evaluating the anatomical relationship between the VA and JB yielded by the three-dimensional reconstruction (3DRC).

16. In the first and second paragraph, the results of MRI evaluations as well as demographics such as gender and age, are provided for the entire cohort. These findings would seem better placed in the 'results' section.

Response: Thank you for your suggestion. We have corrected it.

Results
17. Regarding differences in age or gender among the hydropic and non-hydropic ears, a p value &lt;0.05 is provided whereafter it is stated that no significant differences were found. Please resolve the discrepancy. Additionally, data regarding gender and age is not shown in this article, but a description of these demographics is provided in the second paragraph of the 'materials and methods' section.

Response: Thank you for your suggestion. A p value &lt;0.05 was incorrect in the first paragraph in 'results. We have corrected it, 'P&gt;0.05'. The results of MRI evaluations as well as
demographics such as gender and age have been placed in the 'results' section in the revised manuscript.

18. What was the distribution of clinical diagnoses within your cohort and among hydropic and non-hydropic ears (i.e. how many definite MD and probable MD patients)?
Response: Thank you for your question. We have written the number of definite MD and probable MD patients among hydropic and non-hydropic ears in the 'results' section.

19. What was the level of agreement between radiologists regarding CT analysis (HJB, morphology of JB and VA)?
Response: Thank you for your question. All images obtained by HRCT and MRI were evaluated by two experienced radiologists who were blinded to the diagnosis of all patients. If their evaluations differed, a third radiologist made the final decision.

20. As two hydrops sequences were performed: what was the level of agreement between radiologists and between the 3D-FLAIR and 3D-real IR sequence for the presence (and degree) of EH?
Response: Thank you for your question. In order to uniformly evaluate the membranous labyrinth, 3D-real IR was only used to evaluate hydrops in the revised manuscript.

21. It would be interesting to see the distribution of EH among the hydropic ears with type 4 JB and type 3 HJB. Considering the anatomical location of the endolymphatic duct, one would expect the vestibular compartments to be affected first (i.e. isolated cochlear hydrops would be an unexpected finding).
Response: Thank you for your suggestion. Due to the length of the manuscript, we didn’t list the detail of all clinical information such as the distribution of EH among the hydropic ears with type 4 JB and type 3 HJB, but that’s a question will be further studied in the future.

Discussion
1. In the first paragraph, it is stated that "the anatomical variables detected using HRCT and 3DRC in hydropic and non-hydropic ears were confirmed by Gd-MRI". Do you mean VA and JB morphology was also evaluated at delayed Gd-MRI, in addition to CT analysis? If so, please explain these methods.
Response: Thank you for your question. We had made a descriptive mistake and corrected it. The sentence "the anatomical variables detected using HRCT and 3DRC in hydropic and non-hydropic ears were confirmed by Gd-MRI" was replaced by “the anatomical variables detected using HRCT and 3DRC in the ears with the confirmation of endolymphatic hydrops and no endolymphatic hydrops by Gd-MRI”.

2. In the second paragraph, it is stated that no consensus classification system for JB currently exist. As you have used the classification system for JB by Manjila and Semaan, what are your views on this method?
Response: Thank you for your question. As the VA is located between the common crus and posterior semicircular canal (PSCC), the current proposal of the Manjila and Semaan classification for JB accounts for the relationship of PSCC; therefore, this classification system
for JB is likely to provide an appropriate information for the alterations of the VA morphology related to HJB in MD.

3. Obliteration of the VA by HJB could be used as a radiological sign that indicates HJB as a causative factor for the development of EH and clinical manifestation of MD. What are your thoughts on the clinical utility of this radiological sign? Does this alter treatment strategies?
Response: Thank you for your question. As mentioned in the discussion, page 18, lines 376-384, an obliteration of the VA by HJB could become a causative factor for the development of EH, although the prevalence is low, the identification of this causative factor is very important for both the diagnosis of MD and surgical planning in MD treatment. As discontinuity of the VA, the ES shunting/decompression procedures, which targeted the ES to improve the fluid resorptive functions of the ES, most likely couldn’t work in this patient due to the obliterated VA that separates the ES from the other labyrinthine fluid spaces. As a high degree of interindividual variability exists in the etiology of MD, therefore, the lack of a definite aetiopathogenesis of the disease could result in the differences in treatments. The present study would help better manage disease and potentially help with distinguishing different subtypes of MD.

4. In recent literature, implementation of low-grade vestibular hydrops (isolated distention of the saccule) in visual EH grading systems has yielded high sensitivity and specificity for MD. As a cut-off value of 30% for the presence of vestibular EH was used, do the authors think there could be ears falsely categorized as non-hydropic (false-negatives)? If it is correct to assume you used the classification system for vestibular EH by Wesseler et al, they reported a sensitivity of 50% and specificity of 96% in their article for a clinical diagnosis of MD.
Response: Thank you for your question. There is no consensus on the evaluation of EH up to now. As compared with other methods for assessment of EH, such as low-grade vestibular hydrops (isolated distention of the saccule) in visual EH grading systems, quantitative assessment of EH basing on that described by Wesseler has an advantage of minimizing the interpersonal variability in the assessment of an image. Due to the length of the manuscript, whether the false-negatives of EH present in this cohort will be further studied in the future. Additionally, as compared with the use of IT-Gd alone, the use of IT-Gd and IV-Gd MRI improved the effectiveness of imaging and evaluation techniques for EH, which was likely to explain why the present study showed a higher sensitivity than that by Wesseler et al.

5. It is an interesting hypothesis that HJB may induce EH by obstructing/interfering with the endolympathic duct and sac. As a limitation, it is worth discussing that the presence of JB type 3 and HJB type 4 were scarce among your cohort and larger studies are desirable for further confirmation of current hypothesis.
Response: Thank you for your suggestion. We have rewritten a limitation ‘the presence of JB type 3 and HJB type 4 were scarce among our cohort and larger studies are desirable for further confirmation of current hypothesis’.

Reviewer 2: This manuscript reported a study regarding a topic to investigate the pathological features of vestibular aqueduct (VA) related high jugular bulb (HJB) and explore the possible causeconsequence relation between HJB and endolympathic hydrops (EH), and the potential
specific radiological signs for screening causative HJB in MD. However, this reviewer has some concerns about the study. There some issues that should be clarified and discussed by the authors.

1. Article Title

The title is appropriate.

2. Abstract

Abstract is appropriate. However, there can be only one suggestion for the "Methods" section. Please insert the test that was used in this section of abstract and include p value for the statistical analysis confident interval in the methods section.
Response: Thank you for your suggestion. We have inserted the test that was used in this section of abstract and p value for the statistical analysis confident interval.

3. Introduction: Review of the Literature

The review of the literature is adequate and updated. However, several studies about MD. Are missing, the authors may wish to add those in this section.
Response: Thank you for your suggestion. We have added several studies about MD in the introduction.

4. Statement of Objectives

The objectives are clear.

5. Material and Methods

The methods are clear and detailed.

6. Statistical Analysis

There is no statistical analysis needed.

7. Results

The results are clear. The tables are also appropriate.

8. Discussion

The inferred results are well described.

9. Conclusions

This reviewer agrees with the conclusion drawn in the study.

10. Figures

Appropriate.

11. References

The references are generally good, there are some minor errors which can be corrected.

12. Grammar and Style

Recommend the manuscript be reviewed for spelling, punctuation, and grammar. There are few mistakes in the reference list which should be corrected. is in need of further refinement.

This manuscript reported a study regarding a topic to investigate the pathological features of vestibular aqueduct (VA) related high jugular bulb (HJB) and explore the possible cause consequence relation between HJB and endolymphatic hydrops (EH), and the potential specific radiological signs for screening causative HJB in MD. However, this reviewer has some concerns about the study. There some issues that should be clarified and discussed by the authors.
Given the structure and the base of the study the study can be accepted with minor revision.