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Commentary

Magnetic resonance imaging of endolymphatic hydrops: Controversies and common ground, comment on: "A plea for systematic literature analysis and conclusive study design"

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We have read the comments of Gürkov et al. regarding our paper with great attention. Unfortunately, Gürkov et al. are reluctant to accept the structured methods used in our systematic review that include a pre-defined search strategy, a set of quality criteria for the selection of studies and a main outcome measure (visualization of endolymphatic hydrops).

Magnetic resonance Imaging (MRI) can provide non-specific abnormalities that cannot be associated to a clinical diagnosis in a given patient. The association must be established by prospective case-control studies and the causality by prospective cohort studies with an appropriate sample size to reach enough statistical power in clinical research. Our study limited the search strategy to the last 5 years, since a significant number of studies with moderate sample size were retrieved (13 case-controlled studies with 833 individuals). This is the reason that we did miss 2 case-controlled study published by Grieve [1] that included 12 cases and 2 controls and Liu [2] with 6 cases and 20 controls. However, according to the number of individuals in these two studies, no statistical analysis could be performed.

The selection of studies was conducted according to quality criteria to obtain the best evidence available. For this reason, we selected case-control studies as the main source for synthesis and conclusion generation. Uncontrolled studies can generate hypotheses, but they cannot prove them. Control groups should be sex and age matched to experimental groups and they should be free of any ear or brain pathology to reduce the risk of biases. The use of the contralateral ear in MD or any ear disease as a control is a bias and it is not acceptable in term of study design. So, the studies conducted by Fiorino et al. [3], Hornibrook et al. [4] and Sun et al. [5] compared patients with MD vs. other disorders and were also non-controlled studies.

We agree with Gürkov et al. that we have missed 3 "controlled" studies published by Fukushima [6] that included 11 patients with MD and 3 controls,

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Hagiwara [7] with 10 MD patients and 5 controls, and Homann [8] with 10 MD patients and 2 controls: 10 control individuals in total. These studies were publications with a small number of controls and no matching or statistical analysis is possible with this sample size. The study of Bernaerts et al. [9] was not published when we conducted the search strategy and it could not be included in our review.

The main evidence obtained from our systematic review based on case-controlled studies is that EH can be visualized in most patients with MD, but also in other conditions. The duration of MD is also a major issue, since most of the controlled studies did not report the duration. Further research is needed to determine how many years it takes to develop EH in MD. The EH is the result of damage of the inner ear such as sensorineural hearing loss that could be triggered by different etiologies.

The concept of hydropic ear disease, introduced by Gürkov et al. [10], has been an attempt to move beyond the clinical classification of reference [11] by integrating hydrops imaging data. This is an interesting concept, but it cannot be only associated to MD, because hearing loss itself can also lead to EH. The occurrence of inner ear cellular lesions before EH development was actually demonstrated by pathologists before first imaging publications by the Nagoya group [12]. As stated by Gürkov et al., imaging studies have also generated hypotheses on the relationship between EH and vestibular migraine [13], and more recently between EH and hearing loss threshold in patients with vestibular schwannoma [14]. It reinforces the necessity to distinguish EH evaluation using MRI from MD clinical symptoms. The main implication for clinical practice is that the finding of EH in MRI is a non-specific abnormality and it cannot confirm or replace clinical diagnosis of MD.

So, large imaging datasets should be compared in prospective case-control studies including patients with episodic vestibular symptoms. Further research will confirm the importance of MRI to define endophenotypes and to improve our understanding of the different mechanisms leading to MD.

The current classification, which is based on clinical data, is provisional as long as the relationship between EH and MD symptoms are not fully understood. A future classification encompassing clinical, biological (genetic markers or cytokines), and imaging data in MD will allow a re-classification of vestibular disorders. In this regard, sharing MRI data or technical parameters on an open database would reinforce the role of MRI as a viable method of exploration [15], yet requiring an active participation of many investigators.

Concerning the grading system for the evaluation of EH, several uncontrolled studies have been reported [16, 17], but they cannot be used to classify MD, given the lack of association between EH and MD symptoms.

We agree with authors that the assessment of saccular hydrops without contrast media injection (ie. using T2-weighted imaging) should still be evaluated in more studies. The assumption that this method relies on artifacts seems premature owing to the lack of comparison studies between T2-weighted imaging and contrast media imaging. Simon et al. [18] and Venkastamy et al. [19] have included healthy volunteers to perform quantitative measurement of the saccule, and the use of non-contrast media-based MRI sequences is a major strength of their studies.

We agree that the lack of longitudinal studies evaluated on large multi-center datasets is currently a limitation of all hydrops disease classification. We also agree with Gurkov et al. that MRI is a promising method to identify inner ear liquid variation in patients with undiagnosed audiovestibular symptoms, as was still recently demonstrated in patients with a clinical unilateral vestibular loss [20].

Regarding the conclusions on MRI findings in MD, we would like to remark that there is currently no ideal method of grading for the amount of endolymph. Both the SURI and semi-quantitative method have advantages and drawbacks.

It is interesting to discuss about the correlation between radiological and pathological findings. As stated by Gürkov et al., pathologists have defined endolymphatic hydrops as an "abnormal distension of the endolymphatic space" and not only "an excessive amount of endolymphatic liquid".

However, the semi-quantitative grading system is based on a relative ratio between endolymph and vestibule area without taking into account this notion of distension. An abnormal distension would imply potential compression of nervous structures or modification of biophysical properties of inner ear membranes. The SURI grading system tries to overcome the biophysical modification of the membranous labyrinth in diseased condition, added to the excess of saccular endolymph. We have reported that case-controlled studies using the SURI grading system [21, 22] found half the rate of EH in definite MD in comparison with other studies, in which the grading system was different. A possible explanation can therefore be that both methods do not

evaluate exactly the same imaging biomarker. The newly published criteria of Bernaerts et al. [9] interestingly merged the semi-quantitative grading system with the SURI score, despite the absence of inclusion of utricular protrusion into the lateral semicircular canal.

Our systematic review does not discredit MRI as an emerging tool for research in MD. It firstly outlines the importance of technical parameters (such as the inversion time of the MRI sequences) to evaluate the robustness of a newly proposed imaging sign. We also call for case-controlled studies in inner ear pathologies to generate more evidence for a better understanding and integration of MRI data in the patient management.

The purpose of our review was to evaluate whether MRI may be used for diagnosis of MD. The conclusion is based on the best available evidence: the clinical diagnostic criteria are required and the visualization EH on MRI is not a specific finding for MD.

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