Predicting positive cochlear endolymphatic hydrops on magnetic resonance images

Kao-Tsong Lin MD1 | Chi-Ju Lu MD2 | Yi-Ho Young MD, PhD1

1Department of Otolaryngology, National Taiwan University Hospital, Taipei, Taiwan
2Department of Medical Imaging, National Taiwan University Hospital Yunlin Branch, Yunlin County, Taiwan

Correspondence
Yi-Ho Young, Department of Otolaryngology, National Taiwan University Hospital, 1, Chang-Te St., Taipei, Taiwan.
Email: youngyh@ntu.edu.tw

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Abstract
Objective/hypothesis: This study correlated audiological results with magnetic resonance (MR) images to predict positive cochlear endolymphatic hydrops (EH) on MR images in patients with Meniere's disease (MD).

Study design: Retrospective study.

Methods: Twenty definite MD patients with positive cochlear EH on MR images were assigned to Group A. Another 20 definite MD patients with negative cochlear EH on MR images were assigned to Group B. All patients underwent an inner ear test battery followed by MR imaging using HRDROPS-Mi2 technique.

Results: The mean hearing levels (MHLs) at frequencies of 125, 250, 500 and 1000 Hz revealed significantly worse in Group A than Group B. Significantly deteriorated MHLs were noted from Grades 0 to II at low frequency (125, 250, and 500 Hz), but not at mid-frequency and high frequency. The respective cutoff hearing thresholds at frequencies of 125, 250, and 500 Hz were 27.5, 32.5, and 40 dBHL, which help predict positive cochlear EH on MR images. By using the sum (27.5 + 32.5 + 40 = 100 dBHL) of cutoff thresholds from three low frequencies as a cutoff value, Group A (80%) showed significantly more ears with sum of low-frequency hearing threshold >100 dBHL than Group B (30%).

Conclusion: When sum of three low-frequency (125, 250, and 500 Hz) hearing levels is >100 dBHL, positive cochlear EH may be shown on MR images in definite MD patients. In contrast, those MD patients with sum of three low-frequency hearing levels <100 dBHL, MR imaging should be postponed because resolution of EH may cause negative MR images.

Level of evidence: 4

KEYWORDS
endolymphatic hydrops, HRDROPS-Mi2 technique, Meniere's disease, MR imaging

INTRODUCTION

The endolymphatic hydrops (EH) is characteristically the principle pathological correlate with Meniere disease (MD).1 Studies from 22 temporal bones of MD donors, Okuno and Sando2 reported that EH is most frequently identified in the cochlea with the prevalence of 100%, followed by the saccule (77%), utricle (50%) and semicircular canals (27%). Interestingly, this declining sequence of the prevalence of hydrops...
formation in temporal bone study is consistent with a decreasing order of abnormality rates in the inner ear test battery of MD patients, running from the audiometry, cervical vestibular-evoked myogenic potential (cVEMP) test, ocular VEMP (oVEMP) test, to the caloric test. Since the temporal bones of an MD patient are hard to obtain for confirming the EH, recently developed MR imaging using HYDROPS-Mi2 technique may serve an alternative to identify the EH. However, sensitivity of MR imaging at present for visualizing the EH is lower than histopathological study, as evidenced by a sensitivity of 73%-80% for positive EH on MR images in probable or definite MD patients. One possible reason is that histopathological study could demonstrate distortion of the labyrinthine membrane such as rupture of the Reissner's membrane, collapse of the cochlear duct or vestibular membrane, or labyrinthine fistula following EH breaks, whereas MR imaging could not. 

Clinically, diagnosis of definite MD is based on the guidelines proposed by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) in 1995 and the Barany Society in 2015. However, those with atypical MD or MD patients with asymptomatic hydrops on the opposite ear are seldom correctly diagnosed, unless they develop cardinal MD features in long-term follow up. The rationale for performing MR imaging in an atypical MD patient is because MD and sudden sensorineural hearing loss (SSHL) have significant overlap in symptoms, especially in MD patients with monosymptomatic onset of hearing loss at initial stage, or SSHL patients with vertigo. Additionally, as asymptomatic hydrops on the opposite ear acts a transient state from unilateral MD to bilateral MD, MR imaging thus helps mapping the affected territory of EH.

Recently, correlation between hearing level and the grade of cochlear EH offers a promising way to study the progression of MD. However, not all differentials for EH can be visualized on MR images, leading to various sensitivities and specificities of MR imaging for confirming EH. To lessen clinical-radiological discrepancy, appropriate patient counseling and engagement on MR imaging workup are essential. Hence, this study correlated audiological results with MR images to predict positive cochlear EH on MR images in MD patients.

2 METHODS

From January to December 2021, consecutive 40 patients with unilaterally definite MD were encountered at the neurotological clinic of university hospital. All patients received otoscopy and an inner ear test battery comprising audiometry, cVEMP test, oVEMP test, and caloric test. Diagnosis of MD was based on the guidelines proposed by the AAO-HNS and the Barany Society. Then, MR imaging using HYDROPS-Mi2 technique was performed. Based on the presence or absence of cochlear EH on MR images, all patients were divided into two groups.

Twenty MD patients with positive cochlear EH on MR images were assigned to Group A. Thirteen were males and seven were females, with mean age of 55 ± 10 years. Right and left ears were equally affected. Another 20 MD patients with negative cochlear EH on MR images were assigned to Group B, comprising 11 males and 9 females, with mean age of 55 ± 14 years. Right ear was affected in 12 patients, and left ears in 8 ears. There was no significant difference in terms of age, sex and laterality between the two groups (p > .05, Fisher exact or Chi-square test, unpaired t test). Those patients with middle/inner ear anomaly or infection, noise trauma, head injury, sudden deafness, or posterior fossa tumor/stroke were excluded.

This study was approved by the institutional review board of the university hospital, and all patients signed the informed consent to participate.

2.1 Audiometry

The pure tone average (PTA) is the averaged hearing threshold calculated from four frequencies (500, 1000, 2000, and 3000 Hz). Accordingly, MD stage I means PTA ≤25 dBHL, stage II, 26–40 dBHL, stage III, 41–70 dBHL, and stage IV, >70 dBHL. Abnormal PTA is defined when the PTA is >25 dBHL. The mean hearing level (MHL) indicates averaged hearing threshold at each frequency calculated from all ears.

2.2 Caloric test

Bithermal caloric test was performed and slow phase velocity (SPV) of the caloric nystagmus was measured. When the mean SPV is <7/°s, canal paresis is termed. In addition, canal paresis is also interpreted as difference > 25% between maximum SPV measurements for each ear, when compared with the sum of SPVs from each ear.

2.3 oVEMP and cVEMP tests

The detailed procedure of oVEMP and cVEMP tests was described elsewhere. Briefly, forehead taps were utilized for eliciting oVEMP responses (nI-pl waveform). At least two runs were performed to verify the reproducibility of peaks nI and pl, and oVEMPs results were averaged providing the final response. Conversely, cVEMPs were deemed to be absent when the biphasic waveform was not reproducible. Those with the nI latency >13.0 (norm: 11.4 ± 0.8) ms were interpreted as delayed response.

For eliciting the cVEMP, the operator delivered repeatable taps on the occiput. Subjects were required to keep a background muscle activity of 50 μV. At least two runs were performed to check the reliability of cVEMP (p13-n23 waveform). Those with the p13 latency >17.0 (norm: 14.4 ± 1.3) ms were interpreted as delayed response.

2.4 MR imaging

Each patient received MR imaging (Magnetom Verio, Siemens, Erlangen, Germany) twice, at 0 h and 4 h after intravenous injection of gadodiamide hydrate. All scans utilized HYDROPS-Mi2 technique, that is, by subtracting the positive endolymph image from the positive perilymph image, followed by increasing the contrast-to-noise ratio, separate endolymph, perilymph and surrounding bony structure
within a single type of image can be visualized. MR images were then interpreted by two radiologists who were blinded to the inner ear test results. A third radiologist made a final decision if good agreement is not reached.

The cochlear EH was classified into Grades 0–II. Grade 0 (no hydrops) means no displacement of the Reissner’s membrane of the cochlea. Grade I indicates displacement of the Reissner’s membrane, and the area of the cochlear duct does not exceed that of the scala vestibuli. In contrast, Grade II implies displacement of the Reissner’s membrane with the area of the cochlear duct exceeding that of the scala vestibuli.

The vestibular EH was classified into Grades 0–III. Grade 0 (no hydrops) means area of both saccule and utricle <50% of the vestibule. Grade I means area of the saccule ≥ that of the utricle, but not yet confluent with each other. In contrast, confluence of both saccule and utricle with and without rim enhancement are referred to Grades II and III, respectively.

2.5 Statistical methods

The MHLs between the affected and unaffected ears were compared by paired t test. The MHLs of affected ears between the two groups were compared by unpaired t test. The MHLs of three groups were compared by one-way repeated measures ANOVA test, followed by Bonferroni test. Parameters of clinical course between the two groups were compared by Mann–Whitney test.

The receiver operating characteristic (ROC) curve was adopted for analyzing the relationship between the dependent (presence/absence of EH) and independent (MHL) variables. The optimal trade-off between sensitivity and 1-specificity is termed “cutoff value”. Meanwhile, the area under the curve (AUC) enables direct evaluation of the value of predictors. A p value <.05 indicates a significant difference.

3 RESULTS

3.1 Clinical manifestation

Clinical manifestations in Group A comprised hearing loss, tinnitus and vertigo in all patients (100%), followed by aural fullness (55%), nausea/vomiting (40%), and headache (25%). There was no significant difference in terms of clinical manifestation between the two groups (p > .05, Chi-square of Fisher’s exact test).

The duration of MD, frequency of vertigo, and days since the last vertigo spell to audiometry in Group A, represented as median (range), were 36 (0.25–240) months, 4 (0.5–10) per month, and 2 (1–30) days, respectively. Compared with the respective parameters in Group B, both groups did not significantly differ in these regards (p > .05, Mann–Whitney test, Table 1).

3.2 Inner ear test battery

Group A comprised stages I, II, III and IV in 3, 3, 10, and 4 patients, respectively. Restated, 17 out of 20 affected ears of Group A had PTA >25 dB except three ears with low-tone hearing loss (stage I), accounting for 85% abnormality rate. The cVEMP test displayed normal cVEMP in nine ears, and absent cVEMP in 11 ears (55%). The oVEMP test showed normal oVEMP in 12 ears and absent oVEMP in 8 ears (40%). As regards to the caloric test, normal responses were noted in 16 ears, canal paresis in 3 ears, and caloric areflexia in 1 ear, representing 20% (4/20) abnormality (Table 2). In sum, abnormality rates of the inner ear test battery in Group A ran from the audiometry (85%), cVEMP test (55%), oVEMP test (40%) to the caloric test (20%), showing a significantly declining sequence (p < .001, Cochran’s Q test, Table 2).

Group B consisted of stages I, II, III, and IV in 6, 5, 8, and 1 patients, respectively, accounting for 70% abnormality (stages II to IV) in audiometry. There was no significant difference in the Meniere’s stages between Groups A and B (p > .05; 2 × 4 Chi-square test). Group B also showed a similar decreasing sequence in abnormality rates of the inner ear test battery (p < .001, Cochran’s Q test, Table 2). Running from the audiometry (70%), cVEMP test (70%), oVEMP test (50%) to the caloric test (40%). Comparing the abnormality rates of the respective test, significant difference was not identified between the two groups (p > .05, Table 2).

3.3 MHLs: Groups A versus B

In Group A, the MHLs on the affected ears were 41 ± 16, 47 ± 18, 51 ± 19, 51 ± 25, 47 ± 26, 53 ± 26, and 60 ± 24 dB at frequencies from 125 Hz through 8000 Hz, respectively (Table 3). Compared with the respective MHLs on the unaffected ears, significant deterioration of the MHLs were identified on the affected ears regardless of any frequency from 125 Hz through 8000 Hz (p < .001, paired t test, Table 3).

| Group | Duration of MD (m) | Frequency of vertigo (/m) | Last vertigo to audiometry (d) |
|-------|-------------------|--------------------------|-------------------------------|
| A     | 36 (0.25 ~ 240)   | 4 (0.5 ~ 10)             | 2 (1 ~ 30)                    |
| B     | 12 (0.15 ~ 240)   | 1 (0.1 ~ 12)             | 5 (1 ~ 365)                   |
| p value* | 0.728            | 0.284                    | 0.282                         |

Note: Data are expressed as median (minimum ~ maximum).
Abbreviations: d, day; m, month.
*Mann–Whitney test.
In Group B, the MHLs on the affected ears were 28 ± 19, 28 ± 19, 31 ± 21, 33 ± 21, 44 ± 20, 57 ± 26, and 59 ± 29 dB at frequencies from 125 Hz through 8000 Hz, respectively (Table 2). Like Group A, significantly deteriorated MHLs were also identified on the affected ears compared to the unaffected ears no matter from 125 Hz to 8000 Hz (p <.01, paired t test, Table 3).

Next, MHLs on the affected ears between the two groups were compared. Group A showed significantly worse MHLs than Group B at frequencies of 125, 250, 500, and 1000 Hz (p <.05, unpaired t test, Table 3), but not at those of 2000, 4000, and 8000 Hz (p >.05, Table 3). Restated, cochlear EH on MR images may be clearly demonstrated in those MD ears with greater hearing loss at frequencies of 125–1000 Hz. Subsequently, the MHL of each frequency in relation to grade of cochlear EH was analyzed.

3.4 Grade of cochlear EH versus MHL

MR images on the affected ears of Group A demonstrated cochlear EH Grade I in 9 ears and Grade II in 11 ears. EH was confined at the apical turn in 5 ears, at the basal turn in 2 ears, while both apical and basal turns were affected in 13 ears. Additionally, 12 ears (60%) also showed EH at the saccule and utricle. In contrast, cochlear EH was not identified on MR images in all 20 affected ears of Group B, but EH at the saccule was shown in 2 ears (10%).

The MHLs at 125 Hz revealed 28 ± 19 dB for Grade 0 (no hydrops), 34 ± 15 dB for Grade I, and 47 ± 14 dB for Grade II, exhibiting a significant difference (p <.05, one-way ANOVA test, Table 4). Further, significant difference in the MHL at 125 Hz was noted between Grades II and 0 (p <.05, Bonferroni t test), but not between Grade I and Grade 0/II (p >.05). Similarly, significant differences in the MHLs between Grades II and 0 were also noted at 250 and 500 Hz (p >.05, Table 4). In contrast, the MHLs at frequencies of 1000, 2000, 4000, and 8000 Hz did not show significant difference among three grades (p >.05, one-way ANOVA test, Table 4).

The ROC curve was then adopted for analyzing the relationship between the MHL at each frequency and presence/absence of cochlear EH. Accordingly, the optimal cutoff threshold at 125 Hz was 27.5 dB for predicting positive cochlear EH, with a sensitivity of 77.8%, a specificity of 65%, and an AUC of 0.704 (95% CI: 0.535–
Likewise, the cutoff threshold at 250 Hz was 32.5 dB, and that at 500 Hz was 40 dB (Figure 1). Since the respective cutoff thresholds at 125, 250 and 500 Hz were 27.5 dB, 32.5 dB, and 40 dB, all three low-frequency cutoff thresholds were summed (27.5 + 32.5 + 40 = 100 dB) together to discriminate between positive and negative cochlear EH on MR images. Accordingly, Group A showed 16 (80%) out of 20 ears with sum of three low-frequency hearing levels >100 dBHL, significantly more than 6 (30%) of 20 ears of Group B (p < .01, Chi-square test).

Figure 2 illustrated a 58-year-old male with MD on the left ear. Audiometry revealed sum of the three low-frequency thresholds of 115 dB for the left ear, and MR image demonstrated Grade I EH at the cochlea, but not at the saccule and utricle, of the left ear. Figure 3 showed another 53-year-old MD patient with sum of the three low-frequency thresholds of 185 dB for the right ear, and Grade II EH at the cochlea, saccule and utricle were demonstrated.

4 | DISCUSSION

The recently developed MR imaging using HYDROPS-Mi2 technique enables visualize the EH in vivo. It requires scan twice after an interval of...
of 4 h to let the contrast agent move into the perilymph for enhancement. In contrast, the endolymph in the scala media does not enhance due to blood-labyrinth barrier. Via increasing the contrast-to-noise ratio between the endolymph (hyointense) and perilymph (hyperintense), EH could be clearly demonstrated on MR images. This breakthrough in diagnostic imaging on the EH helps reconsider the amendment to the AAO-HNS guidelines for the definition of MD in 2015, which eliminated the “certain" MD category. Later, Nakashima et al. suggested that “certain” MD could be diagnosed by “definite” MD coupled with positive MR images instead of histopathological confirmation, preserving the category of “certain” MD.

Although EH is the hallmark of MD, other histopathological features i.e., rupture, fistula or collapse of the labyrinthine membrane could also be demonstrated on temporal bones of MD donors, but not on MR images of MD patients. Lin et al. reported that MD patients with recovery of hearing (resolution of EH), immediately after vertiginous episode (rupture of EH), or chronic hearing loss (collapse of cochlear duct), may result in negative cochlear EH on MR images. Hence, indication for engaging on MR imaging in MD patients warrants an issue to investigate.

### 4.1 | Inner ear test battery: Groups A and B

Clinical manifestation and course did not significantly differ between Groups A and B (Table 1), likely due to selection criteria of definite MD. Additionally, both groups showed similar declining sequence of abnormality rates, running from the audiometry, cVEMP test, oVEMP test, to the caloric test (Table 2), consistent with a previous report. Recently, Jeng and Young reported that comparing the declining sequence of inner ear deficits between two inner ear disorders may help determine whether both disorders share a similar mechanism. Hence, diagnoses of definite MD in Groups A and B are acceptable. However, one may question why Group A showed positive cochlear EH on MR images, while Group B did not.

Since hearing threshold is the most readily measured variable, and the variable most related to the natural course of MD, MD patients at various stages thus display different clinical features. At early stage (stage I), fluctuating hearing loss or augmented cVEMP may be attributed to a mechanical, biochemical, or some other reversible causes. In contrast, at late stage (stage IV), permanent morphological changes in hair cells accompanied by collapse of cochlear duct may result in absence of EH on morphological assessment. Since the Meniere’s stage did not significantly differ between Groups A and B, the MHLs between the two groups were then compared.

### 4.2 | MHL: Groups A versus B

The MHLs at frequencies of 125, 250, 500 and 1000 Hz revealed significantly worse in Group A than Group B (Table 3). Additionally, significantly deteriorated MHLs (Table 4) from Grade 0 to Grade II were noted at low-frequency (125, 250, and 500 Hz), but not at mid-frequency (1000 and 2000 Hz) and high-frequency (4000 and 8000 Hz). Furthermore, under ROC curve analysis, the respective cut-off thresholds at frequencies of 125, 250 and 500 Hz were 27.5, 32.5, and 40 dB, which help predict positive cochlear EH on MR images.
In other words, hearing threshold at low-frequency plays a key role to show cochlear EH on MR images. To lessen the individual variances, three low-frequency cutoff thresholds were summed together, that is, $27.5 + 32.5 + 40.0 = 100$ dB, for discriminating between positive and negative cochlear EH on MR images. Figures 2 and 3 illustrate MD patients with sum of three low-frequency hearing levels $>100$ dB, and Grades I and II cochlear EH are identified, respectively.

It is well known that low-tone hearing loss correlated with lesion at the apical turn of the cochlea. Although an apical distention of the cochlear duct represented 15% prevalence as normal variants, fortunately, the opposite unaffected ear (Figures 2 and 3) may serve a control for differentiating whether the apical EH is caused by pathological change or normal variant.

### 4.3 Grade of EH versus MHL

Like cochlear EH of varying severity was shown at various turns histopathologically, different grades of cochlear EH may also be identified at different turns radiologically, and the highest grade of EH was utilized. In this study, cochlear EH from Grades 0 to II revealed significantly deteriorated MHLs at low-frequency (125, 250, and 500 Hz), but not at mid-frequency and high-frequency (Table 4), consistent with a previous report that increased endolymphatic volume of the cochlear duct is in relation to hearing loss. Barath et al. reported that the inter-scalar septum at the apical turn can be confidently identified, which may explain why apical EH of the cochlea was frequently shown on MR images. Additionally, significant difference in the MHL of low-frequency was observed between Grades II and 0, but not between Grades I and 0. The reason is probably because cochlear EH is relatively uniform in Grade II, while commonly slightly nodular in Grade I, making Grade I less identified.

Since human measurement for grading of EH is prone to variability, one may imagine a computer algorithm to measure contrast density gradient between the endolymph and perilymph. However, contrast agent cannot enter the endolymph, alternatively, comparing the ratio between the perilymph and reference area (i.e. pons) may be better than human scoring, which is in evolution.

### 4.4 Clinical relevance

Summing the cutoff thresholds at three low frequency (125, 250, and 500 Hz) $>100$ dB may be predictive of positive cochlear EH on MR images. If not, differential diagnoses including chronic low-tone hearing loss due to collapsed cochlear duct, ruptured hydrops just after vertiginous attack, or SSHL with vertigo should be taken into consideration, and treatment modality is thus altered.

In contrast, those MD ears with sum of three low-frequency hearing levels $<100$ dBHL, MR imaging should be postponed, because cochlear EH may not be identified. For instance, spontaneous resolution of EH may occur in MD patients at early stage, as evidenced by 90% hearing recovery rate in patients with acute low-tone hearing loss. Hence, engaging on MR imaging in such patients should be weighed against negative MR images, leading to clinical-radiological discrepancy. Further advanced technique using ultrahigh resolution of fine structures in the inner ear compartments is essential to promote a wider use of MR imaging in neuro-otology.

### CONCLUSION

When sum of three low-frequency (125, 250 and 500 Hz) hearing levels is $>100$dBHL, positive cochlear EH may be shown on MR images in definite MD patients. In contrast, those MD patients with sum of three low-frequency hearing levels $<100$ dBHL, MR imaging should be postponed because resolution of EH may cause negative MR images.

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### CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

### ORCID

Yi-Ho Young (https://orcid.org/0000-0002-3194-5811)

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