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Role of conventional MD staging in modern era of hydrops MR imaging

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Abstract

Objective/Hypothesis: This study correlated stage of Meniere's disease (MD) with MR imaging of endolymphatic hydrops (EH) to assess the role of MD staging in modern era.

Study Design: Retrospective study.

Methods: Fifty-four MD patients (60 ears) underwent an inner ear test battery and were further confirmed by MR imaging. Sixty MD ears were divided into stages I–IV, and hydrops MR images at each stage were compared.

Results: Hydrops MRI demonstrated that EH at the cochlea with respective Grades 0/I/II were 3/7/1 ears for stage I, 0/5/3 ears for stage II, 1/6/26 ears for stage III and 0/2/6 ears for stage IV. Significant relationship was not identified between MD stage and grades of cochlear hydrops. Similarly, no significant relationship was shown between MD stage and grades of vestibular (saccular/utricular) hydrops. The optimal cutoff value of four-tone average for predicting severe type (Grade II–III) cochlear/vestibular EH was 48 dB, which was within the stage III. Hence, prevalence of severe type (Grade II) cochlear EH in stages III (79%) and IV (75%) was significantly higher than stages I (9%) and II (38%). Similarly, severe type saccular/utricular EH in stages III (64%) and IV (75%) also showed significantly higher than stages I (18%) and II (25%).

Conclusion: Although conventional MD staging fails to correlate with the grades of EH on hydrops MRI, late-stage MD may indicate heightened EH severity in the cochlea and vestibule.

Level of Evidence: 4.

KEYWORDS
endolymphatic hydrops, hydrops MR imaging, inner ear test battery, Meniere's disease

1 | INTRODUCTION

Staging of Meniere's disease (MD) was proposed by American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) in 1995 via the four-tone average of hearing thresholds at 500, 1000, 2000, and 3000 Hz using the worst audiogram during the interval 6 months before treatment.[1] Endolymphatic hydrops (EH) stands as the hallmark in the field of temporal bone histopathology for diagnosing

MD.[2] Okuno and Sando[3] conducted a study involving 22 temporal bones from individuals with MD. Their findings revealed that EH was most prevalent in the cochlea (100%), followed by the saccule (77%), utricle (50%), and semicircular canals (27%). This pattern demonstrated a significant decrease in the occurrence of hydrops formation. Clinically, staging of MD is based on four-tone average of audiometry, primarily due to the high percentage of EH occurring at the cochlea. Additionally, there has been a lack of a characteristic parameter for detecting vestibular hydrops, previously. It is until the development of cervical and ocular vestibular-evoked myogenic potential (cVEMP and oVEMP) tests that both saccular and utricular function can be assessed, respectively.[4,5] Thereafter, a declining sequence of abnormality rates is observed from the audiometry, cVEMP test, oVEMP test, to the caloric test in MD patients, which mirrors the decreasing order of prevalence of EH progressing from the cochlea, saccule, utricle to the semicircular canals in temporal bones of MD donors.[6,7]

Recently developed delayed gadolinium-enhanced 3D FLAIR technique enables the intravenous contrast agent to diffuse into the perilymph, resulting in enhanced image. Naganawa et al.[8] introduced an innovative MR imaging method using "HYDROPS" technique, briefly termed hydrops MRI in this text. This technique has been verified in various research settings, highlighting its potential utility in MD and its variants.[9–13] Nakashima et al.[14] later suggested that histopathological evidence could be replaced by hydrops MRI to confirm the EH, since hydrops MRI enables visualization of EH in vivo. Given that hydrops MRI can provide detailed imaging of EH in both cochlear and vestibular partitions, clinicians may question whether relying solely on the four-tone average (MD staging) is sufficient for accurately assessing the extent of EH within the inner ear compartments. Hence, this study correlated the stage of MD with EH on hydrops MRI to assess the role of conventional MD staging in modern era of hydrops MRI.

2 | METHODS

From 2020 to 2022, consecutive 54 definite MD patients (60 ears) with either cochlear or vestibular EH confirmed by hydrops MRI were enrolled in this study. Diagnosis of definite MD was based on the guidelines proposed by the AAO-HNS and the Barany Society.[1,15]

All patients underwent a comprehensive inner ear test battery, which included audiometry, cVEMP test, oVEMP test, and the caloric test, followed by 3T MR imaging. Thirty were males and 24 were females, with a mean age of 55 ± 13 years. Right ear was affected in 21 patients, left ear in 27 patients and both ears in 6 patients. Subsequently, 60 MD ears were divided into four groups based on their MD stages.

Exclusion criteria consisted of concurrent middle or inner ear infection or anomaly, previous ear surgery, noise trauma, head injury, or posterior fossa lesion. Those MD patients ($n = 9$) who exhibited negative EH on hydrops MRI were also excluded from this study, likely due to factors such as hearing recovery, immediately following a vertiginous episode, or persistence of low-tone sensorineural hearing loss, as indicated in a previous report.[16]

This study was approved by the institutional review board of the National Taiwan University Hospital (202111060RIND), and all patients signed the informed consent to attend.

2.1 | Inner ear test battery

Each patient underwent pure tone audiometry (Rion AA67, Tokyo, Japan). The four-tone average was calculated as pure tone average (PTA) from four frequencies of 500, 1000, 2000, and 3000 Hz. Accordingly, stage I of MD means the four-tone average 0–25 dBHL; stage II, 26–40 dBHL; stage III, 41–70 dBHL; and stage IV, >70 dBHL.[1] The pure tone average >25 dB were defined as abnormal. Canal paresis and caloric areflexia in caloric test were interpreted as abnormal. The specific protocols for the oVEMP and cVEMP tests (Smart EP 3.90 equipment from Intelligent Hearing Systems in Miami, FL, USA) were previously outlined elsewhere.[7,17] Those with absent, reduced or delayed responses in oVEMP/cVEMP test were defined as abnormal.

2.2 | MR imaging

Each patient underwent 3T MR imaging (Magnetom Verio, Siemens, Erlangen, Germany) twice. HYDROPS-Mi2 technique was performed at 0 h and 4 h after intravenous gadolinium (0.2 mL/kg) injection.[8]

The cochlear EH was categorized using a three-grade system proposed by Barath et al.[9] Grade 0 signifies no EH formation. Grade I indicates the displacement of the Reissner's membrane along with an area of the cochlear duct ≤ that of the scala vestibuli. Grade II implies an area of the cochlear duct > that of the scala vestibuli.

In contrast, vestibular EH was classified using a four-grade system as described by Bernaerts et al.[10] Grade 0 (no EH) indicates the area of both saccule and utricle <50% of the vestibule. Grade I implies that area of the saccule ≥ that of the utricle, but they have not yet merged together. Grade II refers to the confluence of both the saccule and utricle with rim enhancement, while Grade III is defined as confluence without rim enhancement.

2.3 | Statistical methods

Comparison of the age among four stages was performed by one-way ANOVA test. The gender ratio, clinical symptoms, and abnormality rates of each test among the four stages were compared by 2×4 Chi-square test. The abnormality rates of the inner ear test battery in each stage were compared by Cochran's Q test. Relationship between MD stages and grades of EH was analyzed by Kruskal–Wallis test.

The receiver operating characteristic (ROC) curve was adopted for analyzing the relationship between the dependent (presence/absence of EH) and independent (four-tone average) variables. The optimal tradeoff 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 significant difference indicates p value <0.05.

3 | RESULTS

3.1 | Clinical manifestation

According to the four-tone average, 60 MD ears were divided by their stages, namely, stage I (0–25 dB) in 11 ears; stage II (26–40 dB) in 8 ears; stage III (41–70 dB) in 33 ears and stage IV, (>70 dBHL) in 8 ears. Restated, most (68%, 41/60) MD ears were referred to stage III-IV.

The mean ages of MD patients were 48 ± 14, 58 ± 14, 55 ± 12 and 55 ± 13 years from stages I through IV, respectively, showing non-significant difference among the four stages ($p > 0.05$, one-way ANOVA test, Table 1). Likewise, there was no significant difference in the gender ratio among the four stages ($p > 0.05$, 2×4 Chi-square test, Table 1).

All MD patients had vertigo, tinnitus and hearing loss, likely due to selection criteria, followed by nausea/vomiting, aural fullness and headache. The prevalence of nausea/vomiting from stages I through IV was 55%, 100%, 76%, and 38%, respectively, exhibiting non-significant difference ($p > 0.05$, 2×4 Chi-square test, Table 1). Similarly, significant difference in the prevalence of aural fullness or headache was not observed among the four stages ($p > 0.05$, 2×4 Chi-square test, Table 1). Hence, clinical manifestation fails to significantly differ from stages I through IV (Table 1).

3.2 | Inner ear test battery

Because 11 ears were classified as stage I (0–25 dB), and the remaining 49 ears were stage II–IV, the abnormality rate of audiometry was thus 83% (49/60).

The cVEMP test showed normal responses in 29 ears, and abnormal (including reduced, absent and delayed) responses in 31 ears, accounting for 52% (31/60) abnormality. The oVEMP test revealed normal and abnormal (including reduced, absent and delayed) oVEMPs in each 30 ears, exhibiting 50% (30/60) abnormality. As regards to the caloric test, normal responses were noted in 37 ears, canal paresis in 18 ears, and caloric areflexia in 5 ears, representing 38% (23/60) abnormality. In sum, abnormality rates decreased from the audiometry (83%), cVEMP test (52%), oVEMP test (50%) to the caloric test (38%), showing a significantly declining sequence ($p < 0.001$, Cochran's Q test), which was consistent with a previous report.[6]

However, in relation to individual MD stage, a declining trend in abnormality rates running from the audiometry, cVEMP test, oVEMP test, to the caloric test was only identified in stage III ($p < 0.001$, Cochran's Q test, Table 2), but not in stages I, II and IV ($p > 0.05$), indicating that stages I, II, and IV fail to reflect the progression of inner ear deficits. Additionally, abnormality rates of the cVEMP, oVEMP or caloric test did not significantly differ among the four stages ($p > 0.05$, 2×4 Chi-square test, Table 2).

3.3 | Hydrops MR imaging

Hydrops MR imaging demonstrated EH at the cochlea in 56 ears (93%), followed by the saccule in 44 ears (73%), utricle in 42 ears (70%) and semicircular canals in one ear (2%), exhibiting a significantly declining sequence of EH running from the cochlea, saccule, utricle, to the semicircular canals ($p < 0.001$, Cochran's Q test), mirroring the decreasing order of abnormality rates from the audiometry, cVEMP test, oVEMP test, to the caloric test.

The correlations between MD stages and grades of EH were subsequently analyzed. Hydrops MR imaging demonstrated that EH at the cochlea with respective Grades 0/I/II were 3/7/1 ears for stage I, 0/5/3 ears for stage II, 1/6/26 ears for stage III and 0/2/6 ears for stage IV. However, significant difference did not exist between MD stages and grades of cochlear hydrops ($p > 0.05$, Kruskal–Wallis test, Table 3). Similarly, no significant difference was identified between MD stages and grades of vestibular (saccular/utricular) hydrops ($p > 0.05$, Kruskal–Wallis test, Table 3).

Via the ROC curve analysis, the optimal cutoff value of four-tone average for predicting the presence of severe type (Grade II) cochlear EH was 48 dB, with a sensitivity of 78.4%, a specificity of 78.3%, and an AUC of 0.816 ($p < 0.01$, Figure 1). Similarly, the cutoff value of 48 dB is also usable to predict severe type (Grade II–III) vestibular EH, with a sensitivity of 74.2%, a specificity of 62.1%, and an AUC of 0.704 ($p < 0.01$, Figure 1). As the cutoff value of 48 dB was within the stage III, stages III (79%) and IV (75%) thus exhibited significantly higher prevalence of severe type cochlear EH than stages I (9%) and II (38%, $p < 0.05$, 2×3 Chi-square test, Table 4).

Since a three-grade system was adopted for classifying the cochlear EH,[9] while a 4-grade system was utilized for evaluating the vestibular EH,[10] to match these two grading systems, Grades II and III of the vestibular EH were pooled together to represent severe

TABLE 1 Comparison of clinical information among four stages of Meniere's disease.

Stage	*N* (ears)	Age (Y)	Sex (M/F)	Nausea/vomiting	Aural fullness	Headache
I	11	48 ± 14	7/4	55%	45%	18%
II	8	58 ± 14	3/5	100%	63%	63%
III	33	55 ± 12	18/15	76%	58%	24%
IV	8	55 ± 13	4/4	38%	25%	25%
p value		0.304[a]	0.722[b]	0.08[b]	0.350[b]	0.479[b]

Note: Data are expressed as mean ± SD.
[a]One-way ANOVA test.
[b]2×4 Chi-square test.

TABLE 2 Comparing abnormality rates of the inner ear test battery among four stages of Meniere's disease.

Stage	*N* (ears)	Audiometry	cVEMP	oVEMP	caloric	*p* value[a]
I	11	0	36%	36%	18%	0.351
II	8	100%	38%	75%	50%	0.053
III	33	100%	64%	52%	39%	<0.001
IV	8	100%	38%	50%	50%	0.087
p value[b]			0.240	0.426	0.419	

Abbreviations: cVEMP, cervical vestibular-evoked myogenic potential; oVEMP, ocular vestibular-evoked myogenic potential.
[a]Cochran *Q* test.
[b]2 × 4 Chi-square test.

TABLE 3 Grades of endolymphatic hydrops in relation to four stages of Meniere's disease.

Stage	*N* (ears)	Cochlea	Saccule	Utricle
		Grade 0/I/II	Grade 0/I/II–III	Grade 0/I/II–III
I	11	3/7/1	5/4/2	5/4/2
II	8	0/5/3	3/3/2	3/3/2
III	33	1/6/26	7/5/21	9/3/21
IV	8	0/2/6	1/1/6	1/1/6
p value[a]		0.392	0.368	0.392

[a]Kruskal–Wallis test.

type. Accordingly, severe type saccular/utricular EH identified in stages III (64%) and IV (75%) also showed significantly higher than stages I (18%) and II (25%, $p < 0.05$, Table 4). Hence, elevated MD stage may increase prevalence of severe type cochlear/vestibular EH.

3.4 | Case presentation

Figure 2 illustrated a 55 years old man who had MD on the left ear, with four-tone average of 71 dB (stage IV) for the left ear, and mild hearing loss (35 dB) for the right ear. Hydrops MRI on the left ear demonstrated Grade II EH at the cochlea, and Grade III EH at the saccule and utricle. Hence, this case confirms that late stage (stage IV) increases the severity (Grade II–III) of the EH.

Figure 3 illustrated a 68 years old man who had MD on the right ear, with four-tone average of 37 dB (stage II) for the right ear, and 21 dB for the left ear. Although this case was at early stage (stage II), hydrops MRI demonstrated severe type (Grade II) EH at the cochlea, saccule and utricle on the right ear, but not on the left ear.

4 | DISCUSSION

4.1 | MD staging

The conventional MD staging system was solely based on the cochlear function, that is, four-tone average or types of audiogram,[1,18] partly because hearing is the most readily measured variable, and partly due to paucity of reliable vestibular indicator previously. Although hearing threshold is most related to the natural course of MD,[18] elevated MD stage fails to correlate with increased age in this study, likely because age onset of MD patients does not mean the exact course of MD. Likewise, clinical symptoms among the four stages also showed non-significant difference (Table 1), probably because various treatment modalities may affect the natural course and manifestation of MD.

The cVEMP test was then developed, introducing a potential use for assessing the saccular function. Since the saccule is the second most frequent site for EH,[3] the augmented, normal, reduced or absent cVEMP responses in MD patients may indicate the saccular pathology demonstrating as an enlarged, normal, reduced or collapsed contour, respectively.[19] Hence, asymmetry ratio of the cVEMP amplitude was also utilized to assess the stage of MD.[20] However, lack of robust evidence fails to confirm the above hypothesis. Fortunately, this gap can now be filled via an inner ear test battery coupled with hydrops MR imaging.

4.2 | Inner ear test battery

A comprehensive inner ear test battery, which includes audiometry, cVEMP test, oVEMP test, and caloric test, has been implemented to evaluate the function of the cochlea, saccule, utricle, and semicircular canals, respectively, providing assessment on the affected territory of the EH in MD patients.[7] Because a declining sequence of inner ear deficits in MD ears correlates with a decreasing order of EH in temporal bone histopathological study,[6] comparing the declining sequence of inner ear deficits between two inner ear disorders may thus help determine whether both disorders share a common underlying mechanism.[21]

This study found that abnormality rate of the inner ear test battery in 60 MD ears decreased from the audiometry, cVEMP test, oVEMP test, to the caloric test, showing a significantly declining sequence from the cochlea, saccule, utricle, to the semicircular canals, which is consistent with a previous report.[6] However, significant difference was not identified in the abnormality rates of the cVEMP, oVEMP or caloric test among the four stages (Table 2), indicating that elevated MD stage is unrelated to the decreased vestibular function.

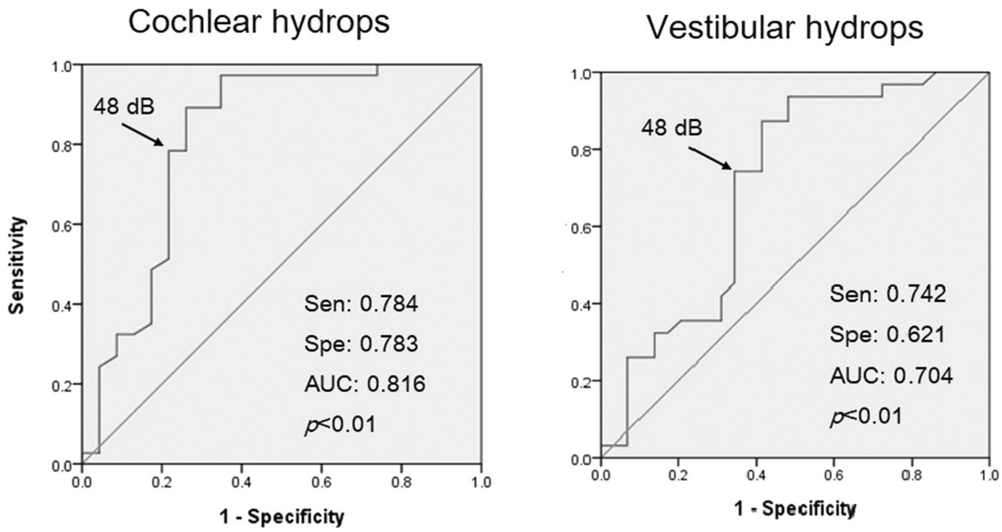

FIGURE 1 The receiver operating characteristic curve demonstrates the optimal cutoff value of four-tone average of 48 dB for predicting severe type cochlear hydrops (Grade II) and vestibular hydrops (Grade II–III).

TABLE 4 Severe type endolymphatic hydrops vs. stages of Meniere's disease.

Stage	*N* (ears)	Cochlea	Saccule	Utricle
		Grade II	Grade II–III	Grade II–III
I	11	1 (9%)[a,b]	2 (18%)[c,d]	2 (18%)[e,f]
II	8	3 (38%)[a,b]	2 (25%)[c,d]	2 (25%)[e,f]
III	33	26 (79%)[a]	21 (64%)[c]	21 (64%)[e]
IV	8	6 (75%)[b]	6 (75%)[d]	6 (75%)[f]
p value[g]		<0.05	<0.05	<0.05

[a–f] $p < 0.05$, 2 × 3 Chi-square test.
[g] 2 × 4 Chi-square test.

Additionally, similar declining trend in the inner ear deficits was only shown in stage III, but not in stages I, II, and IV (Table 2), further supporting that conventional MD staging fails to reflect the progression of inner ear deterioration.

One may ask why not using the video-head impulse test (vHIT) instead of caloric test to evaluate the function of semicircular canals? The caloric test is more likely to identify a deficient horizontal vestibulo-ocular reflex (VOR) in MD patients compared to the vHIT. This is likely due to the fact that caloric test provides low-frequency (0.002–0.004 Hz) stimuli to the horizontal VOR, while vHIT is associated with high-frequency stimuli (5–7 Hz). As the EH enlarges and extends into the endolymphatic space of the horizontal semicircular canal, the caloric response tends to decrease, while the vHIT typically appears normal in such cases.[22]

4.3 | Hydrops MR imaging

The degree of cochlear EH was initially classified into three types, that is, no, mild, and significant hydrops by Nakashima et al.[22] and was later modified as Grades 0 (no hydrops), I (mild hydrops) and II (severe hydrops) by Barath et al.[9] Grades of cochlear EH have been correlated with hearing thresholds at low- and mid-frequency regardless of the grading system utilized.[23] Like histopathological findings, cochlear EH of varying severity was identified at various turns of the cochlea. In such condition, Nakashima et al.[22] suggested using the highest grade of EH on hydrops MRI for interpretation, yet this may not match the cochlear site responsible for the four-tone average from 500, 1000, 2000, and 3000 Hz. Hence, MD stage does not correlate with grades of cochlear EH (Table 3).

One could contend that the enhancement of gadolinium at the cochlear apex is less pronounced in comparison to other turns, posing a difficulty in discerning the apical EH at the cochlea, especially during the early stages of MD.[24] Nevertheless, Yamashita and Schuknecht[25] conducted a study on 495 temporal bones from 300 donors without Meniere's disease (non-MD), revealing an overall incidence of 15.8% for apical EH, indicating that apical EH may be neither pathological nor functional significance. Moreover, the distinct identification of the inter-scalar septum at the apical turn in hydrops MRI could elucidate why apical EH is frequently observed in such imaging studies.[9] Fortunately, the distinction between unilateral or bilateral involvement of apical EH can aid in differentiating whether the apical EH is a result of hydrops itself or simply a normal variant. When apical EH is present in both ears, the likelihood of it being a normal variant increases compared to pathological EH. On the other hand, unilateral apical EH is more likely to be interpreted as pathological. Lin et al.[16] recently reported using the sum of three low-frequency (125, 250, and 500 Hz) hearing levels >100 dB to predict positive cochlear EH on hydrops MRI. In contrast, hydrops MR imaging should be postponed if <100 dB, since small-sized EH may be overlooked.

Subsequently, the ROC curve was adopted to determine the optimal cutoff value of four-tone average for identifying severe type (Grade II–III) EH. Accordingly, a cutoff value of four-tone average >48 dB may predict the presence of severe type EH regardless of

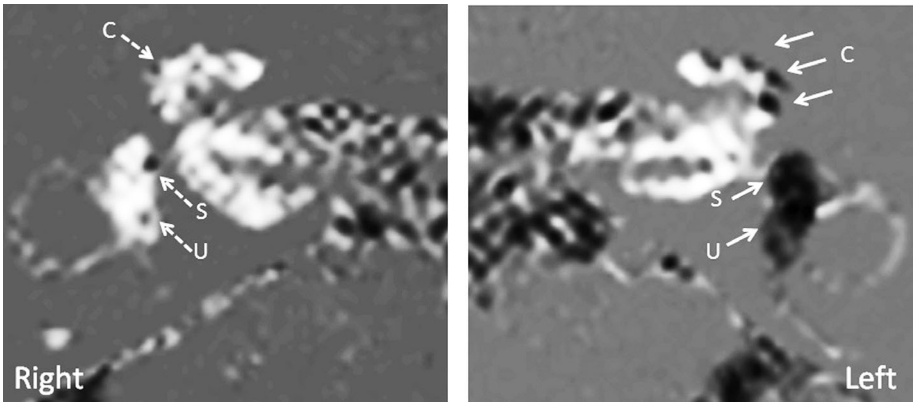

FIGURE 2 A 55 years old man of MD on the left ear, with four-tone average of 71 dB (stage IV). Hydrops MRI on the left ear demonstrates Grade II hydrops at the cochlea (C), and Grade III hydrops at the saccule (S) and utricle (U). Right ear, control. Solid arrows: present hydrops; dashed arrows: no hydrops.

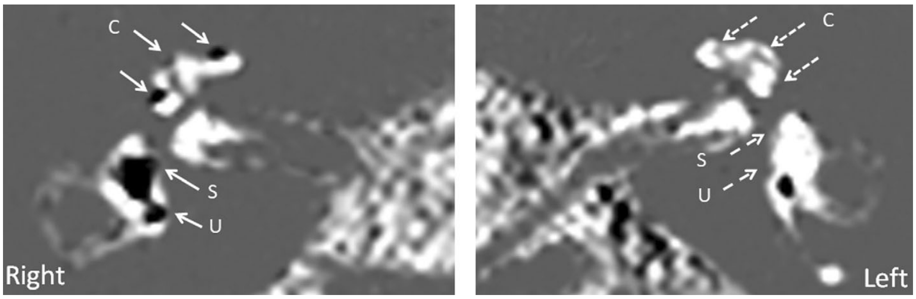

FIGURE 3 A 68 years old man with MD on the right ear with four-tone average of 37 dB (stage II). Hydrops MRI demonstrates Grade II hydrops at the cochlea (C), saccule (S) and utricle (U) of the right ear. Left ear, control. Solid arrows: present hydrops; dashed arrows: no hydrops.

cochlear or vestibular EH (Figure 1). Since the cutoff value of 48 dB was within the stage III, prevalence of severe EH at stages III and IV were analyzed, which exhibited significantly higher prevalence of severe cochlear or vestibular EH than stages I and II (Table 4). Temporal bone histopathological study also revealed that severity of EH correlates with severity of hearing loss.[3] Similarly, Sluydts et al.[26] reported that only the highest grades of cochlear and vestibular EH were related to the declined cochleovestibular function. Our study is consistent with these reports.[3,26]

Restated, coupled with an inner ear test battery, when an MD patient at stage III–IV, severe type EH at the cochlea and/or vestibule may be shown on hydrops MRI (Figure 2), but not vice versa (Figure 3). The late MD stage (stage III–IV) may indicate increased severity of EH at the cochlea/vestibule. Thus, the role of conventional MD staging in the modern era of hydrops MRI is to predict the severity of EH at the late stage.

4.4 | Limitation of the study

Limitation of this study is that patients in this study were recruited from a single medical center, and contained a relatively low sample size. Further large samples studied in this fashion may verify our hypothesis.

5 | CONCLUSION

Although conventional MD staging fails to correlate with the grades of EH on hydrops MRI, late-stage MD (stage III-IV) may potentially serve as an indicator of heightened EH severity in the cochlea and vestibule. Hence, the role of conventional MD staging in the modern era of hydrops MRI appears to be predicting the severity of EH specifically in its late stages.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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