testing has been utilized to estimate endolymphatic hydrops, but these do not give direct proof [1]. These limited options of clinical diagnosis and functional testing were all that were available, thus making precise diagnosis of MD difficult.

Accordingly, visualization of endolymphatic hydrops by 3D-FLAIR of MRI, in association with GBCAs enhancement, will be a breakthrough, giving us a powerful tool to confirm endolymphatic hydrops.

The present imaging data demonstrated that cochlear MD is a continuum disease of classical MD; both being characterized by endolymphatic hydrops. Although further study will be necessary to reach any conclusions, in the near future the diagnostic criteria for MD may be reclassified according to image-based diagnosis.

Furthermore, this study is the first to successfully demonstrate the change in the degree of endolymphatic hydrops in the same subject before and after treatment. Quantitative analysis by bilateral administration of GBCAs with 3.0T-MRI is beneficial to such evaluation. Among several treatment choices, the present results demonstrated direct evidence of the change in endolymphatic hydrops, which may be due to the response to therapeutic agents, i.e. osmotic diuretics (isosorbide). Since the possibility remains that these results were a matter of a natural course, a further large cohort study will be necessary. However, this study demonstrated that MRI-based imaging has a great potential to be a powerful tool not only for precise diagnosis of MD and its variants, but also in therapeutic evaluation of endolymphatic hydrops.

Ac nowled ements

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ORIGINAL ARTICLE

Semi-quantitative evaluation of endolymphatic hydrops by bilateral intratympanic gadolinium-based contrast agent (GBCA) administration with MRI for Meniere's disease

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Abstract

Conclusion: Bilateral intratympanic administration of a gadolinium-based contrast agent (GBCA) in MRI was successfully performed and proved to be beneficial in the semi-quantitative evaluation of endolymphatic hydrops. Such image-based diagnosis will lead to re-revaluation and reclassification of the diagnostic criteria for Meniere's disease (MD). Objective: To visualize endolymphatic hydrops semi-quantitatively in patients with MD, by using bilateral intratympanic GBCA administration with MRI. Patients and methods: A total of 13 patients were evaluated, including 12 with MD and one with acute low-tone sensorineural hearing loss. Diluted gadodiamide (a kind of GBCA) was administered to the bilateral tympanic cavity by injection through the tympanic membrane. After 24 h, the endolymphatic hydrops was evaluated with a 3.0 T MR scanner. The areas enhanced by gadodiamide were measured semi-quantitatively. Results: Three-dimensional, fluid-attenuated inversion recovery (3D-FLAIR) MRI showed that the gadodiamide successfully penetrated the round window membrane, entering the perilymphatic space and delineating the gadodiamide-enhanced perilymphatic and gadodiamide-negative endolymphatic spaces of the inner ear. All the patients with MD showed a reduced gadodiamide-enhanced area representing the perilymphatic space, and the quantitative ratio was 0.15 to 0.85. Furthermore, endolymphatic hydrops was also demonstrated in the patient with atypical MD who had fluctuating low frequency sensorineural hearing loss without vertigo.

Keywords: Endolymphatic hydrops, Meniere's disease, semi-quantitative analysis, gadolinium, gadolinium-based contrast agent (GBCA), MRI

Introduction

Meniere's disease (MD) is an idiopathic disorder of the inner ear characterized by fluctuating sensorineural hearing loss (SNHL), tinnitus and aural fullness, and recurrent spontaneous episodic rotational vertigo (see Sajjadi and Paparella for review [1]). MD has been thought to be attributable to endolymphatic hydrops, but this has only been confirmed histopathologically after death. Therefore, MD has been diagnosed on the basis of clinical symptoms and is classified into typical MD with all cochlear and vestibular symptoms, and atypical MD with either cochlear symptoms (e.g. hearing loss, tinnitus, aural pressure) or vestibular symptoms (e.g. vertigo alone with aural pressure) [2]. Typical MD can further be classified into certain, definite, probable, and possible MD according to the nature of the hearing loss, tinnitus, aural fullness, and vertigo [2]. In addition, clinical diagnosis has sometimes been hampered by other conditions that closely resemble MD, such as acute low tone sensorineural hearing loss (ALSNHL) [3]. Therefore, along with clinical symptoms, clinical tests suggestive for endolymphatic hydrops are usually used for diagnosis. Functional

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testing including electrocochleography (EcochG) or glycerol test has been used to estimate endolymphatic hydrops [1]. However, even if functional testing is performed, the results are still indirect proof.

Recent advances in imaging by three-dimensional, fluid-attenuated inversion recovery (3D-FLAIR) of magnetic resonance imaging (MRI), in association with enhancement by gadolinium-based contrast agents (GBCAs), enables visualization of endolymphatic hydrops in patients with MD [4 6]. In the present study, involving patients with typical MD, atypical MD, and ALSNHL, we evaluated endolymphatic hydrops in a semi-quantitative manner, through comparison of bilateral perilymphatic spaces enhanced by a GBCA.

Patients and methods

Sub ects

Ten patients with 'definite' MD and one with 'possible' MD who met the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) criteria, one patient with atypical MD (who had fluctuated low frequency sensorineural hearing loss without vertigo), and one patient with acute low-tone sensorineural hearing loss (ALSNHL) participated in this study.

MRI

Gadodiamide (Omniscan, Daiichi Pharmaceutical Co. Ltd, Tokyo) was diluted eightfold with saline, and 0.4 0.6 ml of the diluted gadodiamide was administered to the bilateral tympanic cavity by injection through the tympanic membrane using a 23 G needle. The injection was carried out under a microscope. The patient then lay down in the supine position for 60 min. After 24 h, the endolymphatic hydrops was evaluated by MRI. We used a 3.0 T MR scanner (Trio, Siemens, Erlangen, Germany) with a receive-only eight-channel phased-array coil. It can perform T1-weighted three-dimensional (3D) magnetization prepared rapid gradient echo (MP-RAGE). The parameters for MP-RAGE were: TR 1500 ms, TE 3 ms, matrix size of 320 290 320; 72 axial 0.8 mm thick slice, 0.8 mm 0.8 mm 0.8 mm isotropic voxels, heavily T2-weighted 3D-TSE sequence, and 3D fluid-attenuated inversion recovery (FLAIR) with variable flip angle echo train (SPACE). The parameters for heavily T2-weighted SPACE were: TR 1350 ms, TE 199 ms, echo train length (ETL) 93, matrix size of 320 288 278, 56 axial 0.8 mm thick slice, and voxel size of 0.6 0.4 0.8 mm. In addition to the methods described previously, we used 3D-FLAIR with higher in-plane spatial resolution. The scan parameters for the 3D-FLAIR sequence were as follows: repetition time of 10 000 ms, echo time of 666 ms, inversion time of 2500 ms, single slab 3D turbo spin echo with variable flip angle distribution, echo train length of 173, matrix size of 320 320, 52 axial 0.8 mm thick slices to cover the labyrinth with a 20 cm square field of view, acceleration factor of two using the parallel imaging technique, and generalized autocalibrating partially parallel acquisitions. Voxel size was 0.7 0.8 0.8 mm. The number of excitations was one and the scan time was 9 min.

The multi-planar reconstruction (MPR) image was created from 3D-FLAIR images by imaging analysis software (Aquarius Net Viewer). The areas enhanced by gadodiamide in the cochlea and vestibule were traced and measured on the image in the plane perpendicular to the modiolus. Then, the affected side/contralateral side ratios were calculated (Figure 1). Semi-quantitative comparison of endolymphatic space in the vestibule was also calculated using Dicom Viewer software (EV Insite).

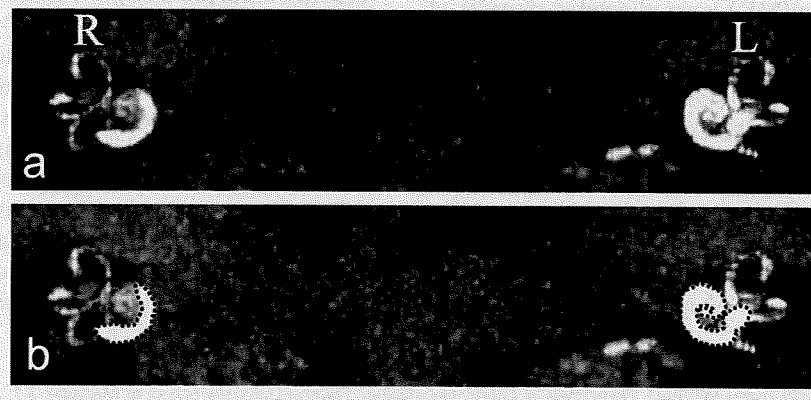

Figure 1. The areas enhanced by gadodiamide in cochlea and vestibule were measured using multi-planar reconstruction (MPR) image by imaging analysis software (dotted lines), and the affected side/unaffected side ratios were calculated.

Clinical testing

Pure tone audiometry (PTA) was performed before and after the experiment. The average of 0.5, 1, 2, and 4 Hz is shown in Table I. For vestibular testing, caloric testing and vestibular-evoked myogenic potential (VEMP) testing were performed. In caloric testing, maximum slow eye velocity was measured by cold water irrigation (20°C, 5 ml, 20 s). In VEMP testing, the electrographic signal from the stimulated side was amplified and averaged using a Neuropack evoked potential recorder (Nihon Kohden Co. Ltd, Tokyo, Japan). Clicks lasting for 0.1 ms at 105 dBnHL were presented through a headphone. The stimulation rate was 5 Hz, the band-pass filter intensity was 20–2000 Hz, and analysis time was 50 ms. The responses to 200 stimuli were averaged twice.

The Ethics Review Committee of Shinshu University School of Medicine approved the protocol of the study and all patients gave their informed consent to participation.

Results

In this study, 3D-FLAIR MRI clearly showed that the gadodiamide successfully penetrated the round window membrane, entered the perilymphatic space, and delineated the gadodiamide-enhanced perilymphatic and gadodiamide-negative endolymphatic spaces of the inner ear. The endolymphatic space is comparatively small and difficult to identify as a vacant area in the normal side. In contrast, the endolymphatic space in an ear with endolymphatic hydrops is partially or entirely expanded, making identification of the endolymphatic space easier (Figures 2 and 3).

Gadodiamide distribution patterns within the inner ear were variable and differed individually. In patient no. 3, who had definite MD, after 24 h the intratympanic gadodiamide moved toward the perilymphatic space, and the endolymphatic hydrops could be detected as a black area surrounded by the perilymphatic space filled with the gadodiamide in the basal turn of the left cochlea (Figure 2). In the unaffected side, the endolymphatic space (which was significantly small) may have been masked by the strong enhancement of perilymphatic space. In patient no. 6, who also had definite MD, the endolymphatic space in the vestibule on the affected side was significantly larger than that on the normal side (Figure 3). In this patient, in association with the imaging, VEMP was absent, but the caloric test showed normal response.

Table I summarizes imaging results and clinical data obtained for each patient. In the cases such as no. 3 or 6 mentioned above, endolymphatic hydrops could be easily identified qualitatively. However, in some cases, it was difficult to obtain supportive imaging for endolymphatic hydrops. Therefore, the present study tried to perform semi-quantitative analysis by using the MPR image, created from 3D-FLAIR images. Based on the semi-quantitative analysis, the gadodiamide-enhanced area representing the perilymphatic space ratio was 0.14 to 3.86 (Table II). In 9 of 10 patients with definite MD the ratio was reduced, and the quantitative ratio was 0.15 to 0.85 (Table II). In the exception, patient no. 4, gadodiamide was not introduced in the perilymphatic space even on the normal side, probably due to technical failure.

Table I. Summary of bilateral intratympanic gadolinium administration.

Patient no.	Age/sex	Diagnosis	Side	Caloric test CP%	VEMP	PTA-pre (dB) Affected side	PTA-pre (dB) Unaffected side	PTA-post (dB) Affected side	PTA-post (dB) Unaffected side
1	51/M	MD	R	7.2	Depressed	38.8	15.0	38.8	15.0
2	41/F	MD	R	51.2	–	37.5	11.3	32.5	11.3
3	42/M	MD	L	41.3	Depressed	50.0	12.5	53.8	12.5
4	42/F	MD	L	19.9	ND	33.8	12.5	32.5	10.0
5	76/F	MD	L	39	ND	46.5	30.0	40.0	27.5
6	51/F	MD	R	11.9	Absent	22.5	13.8	28.8	12.5
7	53/M	ATMD	R	–	–	58.8	13.8	47.5	13.8
8	38/M	MD	R	22.6	Depressed	20.0	6.3	28.8	5.0
9	76/M	ALSNHL	R	–	–	17.5	46.3	13.8	43.8
10	67/F	MD	L	6.9	ND	55.0	28.8	52.5	26.3
11	52/F	MD	L	6.8	ND	65.0	12.5	62.5	13.8
12	53/F	MD	L	42.3	Depressed	53.8	22.5	47.5	20.0
13	33/M	pMD	R	50.6	Normal	12.5	6.3	6.3	6.3

ALSNHL, acute low tone sensorineural hearing loss; ATMD, atypical Meniere's disease; F, female; L, left; M, male; MD, 'definite' Meniere's disease; ND, not detectable; pMD, 'possible' Meniere's disease; PTA, pure-tone audiometry; R, right.

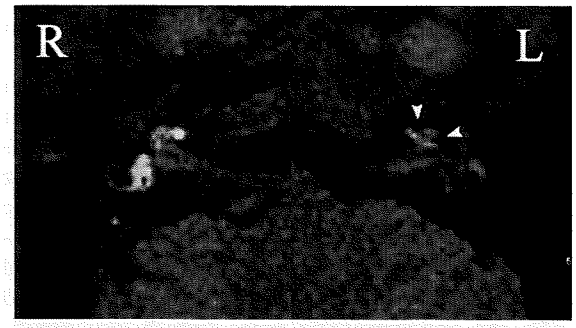

Figure 2. MRI imaging in patient no. 3 (definite Meniere's disease). The endolymphatic hydrops is detectable as a black area (arrowheads) inside the perilymphatic space filled with the gadodiamide in the basal turn of the left cochlea. In the normal side, the endolymphatic space (a significantly small area) is not detectable, probably due to strong signal intensity in the perilymphatic space.

We measured the saccular endolymphatic space by bilateral comparison. Eleven of 13 patients, including 8 with definite MD, 1 with possible MD, 1 with atypical MD, and 1 with ALSNHL, showed differences in endolymphatic space in the saccules. Significant differences (Student's *t* test) in patient nos 6, 8, 10, and 11 were noted (Figure 4)

Concerning vestibular functional testing, caloric testing was performed in all but two patients (nos 7 and 9), and showed decreased response in five cases. VEMP testing was performed in all patients, except nos 2, 7, and 9. In 6 of the 10 patients who underwent the testing, VEMP was either absent on the affected side or depressed compared with the healthy side. VEMP amplitude could not be obtained because of low muscle contraction in patient nos 4, 5, and 10.

No adverse effects, such as vertigo, hearing deterioration, or tinnitus due to the intratympanic injection of gadodiamide were observed and there were no changes in hearing level (Table I).

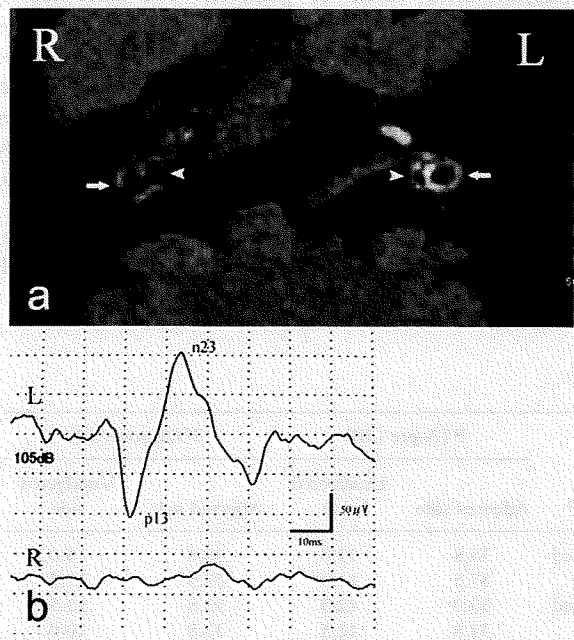

Figure 3. MRI imaging in patient no. 6 (definite Meniere's disease). The endolymphatic space in the saccules is detectable as a black area inside the perilymphatic space filled with gadodiamide in the vestibule (arrowheads). In the normal side (L), the endolymphatic space in the saccules is also detectable in the unaffected side, but is smaller than in the affected area. Arrows indicate lateral semicircular canals. In the affected side (R), enhancement by gadodiamide was weaker than in the unaffected side, indicating that endolymphatic hydrops may be present in the canal. VEMP testing showed no response in the affected side.

Discussion

The hallmark of MD diagnosis is to prove endolymphatic hydrops, but this has been achieved only in temporal bone histopathology after death. Initial attempts to identify endolymphatic hydrops involved visualization of the Reissner membrane, and it was successfully visualized in animals [7] and human cadavers [8]. The subsequent attempts to identify endolymphatic hydrops used intratympanic GBCA administration with 1.5 T MRI to visualize the

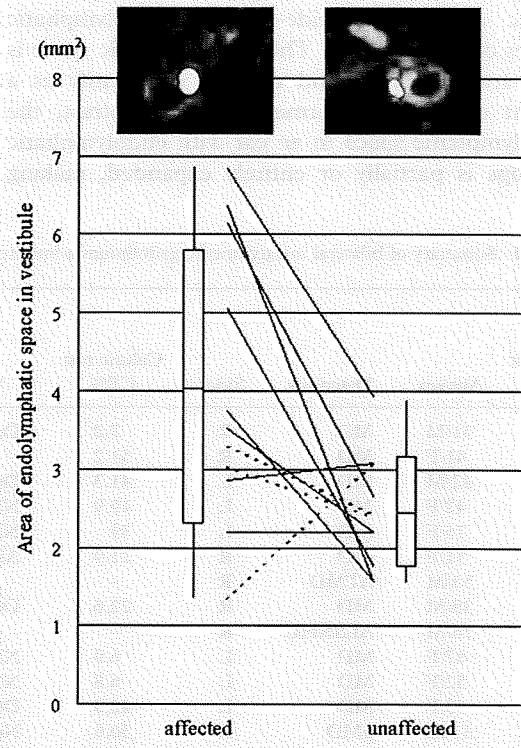

Figure 4. Semi-quantitative analysis of bilateral endolymphatic space in the sacculus.

Table II. Gadolinium distribution in inner ear.

Patient no.	Affected side			Unaffected side			Area		Ratio	Area (vestibule)	
	Cochlea	Vestibule	Semicircular canals	Cochlea	Vestibule	Semicircular canals	Affected side	Unaffected side		Affected side	Unaffected side
1	Basal, second, apical	Whole	Whole	Basal, second, apical	Whole	Whole	17.6	26.8	0.65	2.86	3.08
2	Basal, second, apical	Whole	Whole	Basal, second, apical	Whole	Whole	18.5	21.9	0.85	2.2	2.2
3	Basal, second, apical	Whole	Whole	Basal, second, apical	Whole	Whole	19.6	36.8	0.53	3.74	1.57
4	Faint	Faint	Faint	Faint	Faint	Faint	4.9	1.3	3.86	–	–
5	Basal	Whole	Partial	Basal	Whole	Partial	15.9	19.7	0.81	–	–
6	Faint	Faint	Partial	Basal, second	Whole	Partial	4.6	30.8	0.15	6.84	3.92
7	Basal	Faint	Whole	Basal, second, apical	Whole	Whole	15.0	30.0	0.50	3.02	2.38
8	Basal, second, apical	Whole	Whole	Basal, second, apical	Whole	Whole	20.4	25.6	0.80	6.37	1.54
9	Basal, second	Whole	Whole	Basal, second, apical	Whole	Whole	26.1	27.6	0.95	3.3	2.42
10	Basal, second, apical	Whole	Whole	Basal, second, apical	Whole	Whole	18.1	33.1	0.55	5.05	1.76
11	Basal, second, apical	Whole	Whole	Basal, second, apical	Whole		10.7	20.1	0.53	6.15	2.64
12	Basal, second	Faint	Whole	Basal, second, apical	Whole	Whole	5.6	25.2	0.22	3.52	2.2
13	Basal, second, apical	Whole	Whole	Basal, second, apical	Whole	Whole	21.2	20.9	1.01	1.32	3.08

endolymphatic/perilymphatic space [9]. Recent advances in imaging technology enabled visualization of human endolymphatic hydrops by intratympanic Gd-DTPA administration at 3.0 T MRI [4–6]. The present study adds supportive evidence that endolymphatic hydrops can be diagnosed by the same protocol and expands the findings by semi-quantitative analysis. As in the previous reports [4–6], we could recognize the existence of endolymphatic hydrops as a decreased perilymphatic space, which may indicate an expanding endolymphatic space. Furthermore, semi-quantitative evaluation based on the ratio of the GBCA-enhanced area between affected/control sides represents the degree of endolymphatic hydrops.

In all 10 patients who had definite Meniere's disease, except for 1 (patient no. 4 with failure due to technical error), the ratio was reduced, and the quantitative ratio was 0.14 to 0.85. The present data are the first to indicate that bilateral intratympanic administration of GBCAs is beneficial in the semi-quantitative evaluation of endolymphatic hydrops.

There was inter-individual variation in the pattern of gadodiamide enhancement. For example, in patient no. 3, endolymphatic hydrops was predominantly detected in the cochlea (Figure 2). In contrast, vestibular hydrops was predominantly identified in patient no. 6 (Figure 3), in whom no VEMP response was found, suggesting that imaging findings are well correlated with the functional testing. A series of temporal bone studies also demonstrated that endolymphatic hydrops occurs either locally or entirely [10]. In the cochlea, the endolymphatic space is too small to recognize compared with the perilymphatic space, therefore endolymphatic space is usually undetected in the normal side. Thus, the existence of endolymphatic hydrops, which indicates abnormality, can be qualitatively identified more easily. In contrast, saccular endolymphatic spaces can be identified even in normal ears, making precise diagnosis for endolymphatic hydrops difficult without bilateral comparison. An additional advantage of the present procedure of bilateral intratympanic injection of a GBCA is the enablement of semi-quantitative comparison of endolymphatic space in the vestibule, which is difficult to evaluate by unilateral injection. In this study, four cases with definite MD showed significant differences in endolymphatic space in the saccular region and all of these patients (except patient no. 10 who could not be analyzed due to incomplete myogenic compression) showed decreased response. These correlations between imaging of sacculus associated with saccular functional testing such as VEMP will be of great help in precise diagnosis as well as therapeutic choice in MD.

In the present study, 6 of 11 patients who underwent caloric testing showed unilateral vestibular hypofunction. In comparison with VEMP, in some patients (nos 3, 8, and 12) both were decreased, but the others were shown to be abnormal in VEMP whereas normal in caloric responses (nos 1 and 3). Such discrepancy between the two testing methods, i.e. normal caloric test which is a function of the lateral semicircular canal, and a decrease in or disappearance of VEMP, has recently been reported in MD [11,12]. The present study confirms the saccular hydrops by imaging as well as VEMP, supporting the existence of such pathological conditions. In addition to general quantification, the advantage of bilateral intratympanic injection of GBCAs is semi-quantitative evaluation of saccular endolymphatic hydrops.

No adverse effects, such as vertigo, tinnitus, or hearing deterioration, were noted after intratympanic injection of gadodiamide, indicating that the present protocol can be safely performed in ordinary clinical settings. This is also supported by a recent study using guinea pigs in which diluted GBCAs had no apparent effects on endocochlear potential [13].

EcochG and glycerol testing have been widely performed as useful, but indirect, tests for the detection of endolymphatic hydrops in MD. Because these are indirect tests, EcochG or glycerol testing cannot play a decisive role in determining the presence or absence of endolymphatic hydrops. Unfortunately, in this study, systemic comparison between these tests and imaging results could not be performed. Therefore, a final conclusion concerning the relationship between these previous findings and the current MRI findings await future systemic comparative study.

The number of cases other than MD in this study was limited, and the etiology of each category of disease was not conclusive. In previous studies, 8.5% of patients with ALSNHL progressed to 'definite' MD [14], indicating that some MD was previously diagnosed as ALSNHL. In this study, the patient with ALSNHL was not associated with endolymphatic hydrops. Future study using many cases will subclassify ALSNHL whether it is associated with endolymphatic hydrops or not.

In this study, endolymphatic hydrops was also demonstrated in the patient with atypical MD who had fluctuated low frequency sensorineural hearing loss without vertigo, indicating the possibility that some atypical MD is a continuum clinical entity of MD. Therefore, in the future, the diagnostic criteria for MD may be expanded and reclassified according to image-based diagnosis.

In conclusion, bilateral intratympanic administration of a GBCA was successfully performed and

proved to be beneficial in the semi-quantitative evaluation of endolymphatic hydrops.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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