を内耳における薬物の拡散に着目して検討を行うことにした。

## B. 方法

６名のゲンタマイシン治療を受けたメニエール病患者を対象とした。ガドリニウム鼓室内投与にあたっては倫理委員会の方針に沿い同意書にサインしてもらった。ガドリニウム造影剤（Omniscan, Daiichi Pharmaceutidcal Co. Ltd, Tokyo, Japan）を生食にて 8 倍に希釈し鼓室内に注入した。注入後は１時間、注入側を上にしてできるだけ嚥下しないようにしてもらった。注入方法等は過去のわれわれの報告に準じている[1]。

## C. 結果

６名のメニエール病患者において、内耳に移行したガドリニウムの分布状態には、かなりの個人差が認められた。内耳自体への移行が悪い例や前庭・半規管への移行が悪い例が認められた。内耳自体への移行が悪い例は、正円窓の透過性が悪く、前庭・半規管への移行が悪い例は、前庭の内リンパ水腫が顕著でガドリニウムが通る前庭外リンパのスペースがほとんどないためと考えられた。症例１に、前庭・半規管への移行が悪い例を示す。症例２は、内リンパ水腫はあったが、ガドリニウムの半規管への移行は良かった例である。

## D. 考察

近年、メニエール患者の治療に対してゲンタマイシンの鼓室内投与が多く行われるようになってきた。しかし、その投与回数や投与期間についてどのようにしていったらよいか一定の見解はまだない。メニエール患者においてゲンタマイシンを投与しても効果の出ない患者がおり、数回のゲンタマイシンの投与によって、メニエールの症状が改善されず、聴力が低下してしまうことがある。可能性として、ゲンタマイシンが何らかの内耳の問題によって、前庭ではなく、蝸牛へ移行し、聴力を低下させてしまった可能性が考えられていたが、今回の結果から、前庭内リンパ水腫が極めて高度で外リンパのスペースが無く、せっかく投与したゲンタマイシンが前庭に入らず、ほとんど蝸牛に入り、めまいに対する効果が無く、聴力が低下することもありうることが示された。

## E. 結論

鼓室内ガドリニウム注入後の MRI は、鼓室内ゲンタマイシン治療の効果の予測に有用であることが示唆された。

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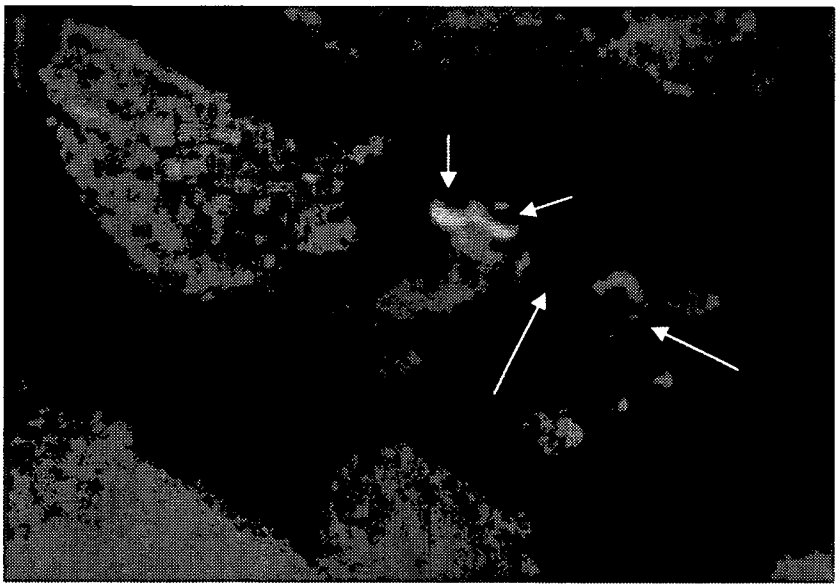
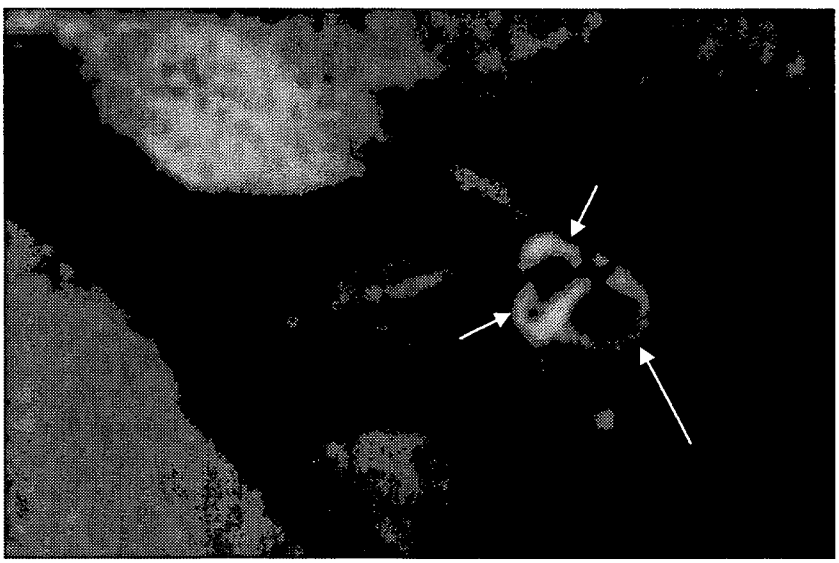


症例1
短い矢印は蝸牛基底回転における水腫部位を表している。ガドリニウムの前庭と三半規管への移行は乏しい（長い矢印)。



症例2
ガドリニウムの三半規管への移行は良好な例。前庭に水腫はあるが、前庭の外リンパが、その水腫を一周している（短い矢印)。長い矢印は外側半規管。

厚生労働科学研究費補助金（感覚器障害研究事業）
分担研究報告書

# 病理標本からの内外リンパ腔三次元モデルの作成

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## 研究要旨

現在まで、内リンパ水腫の病理標本からの内耳三次元モデルの作成と体積測定は我々の渉猟しえた限り報告はない。我々は、ミネソタ大学にて撮影した側頭骨病理標本7例（内リンパ水腫2例、コントロール5例）を用いコンピュータによる解析を試みた。標本は1スライスにつき20ミクロンの厚さとし、200ミクロンごとにスライスを重ね解析ソフト（ZedView）を用いて三次元化を行った。また、内外リンパ腔の体積測定も同時に行った。三次元化した内耳モデルは、画像編集ソフト（FreeForm）を用いてスムージングを行った。

## A. 研究目的

内耳は、迷路といわれるようにその形態は複雑であり、内リンパ、外リンパがどのような構造となっているかを立体的に把握することは困難である。そこで、今回、我々は実際の側頭骨標本から画像を取り込み、コンピュータ処理にて三次元化し体積測定を試みた。

## B. 研究方法

ミネソタ大学にて撮影した側頭骨病理標本7例（内リンパ水腫2例、コントロール5例）を用いコンピュータによる解析を行った。標本は1スライスにつき20ミクロンの厚さであり、200ミクロンごとに撮影した。撮影スライスを重ね解析ソフト（ZedView）を用いて三次元化を行った。また、内外リンパ腔の体積測定も行った。三次元化した内耳モデルは、画像編集ソフト（FreeForm）を用いてスムージングを行った。

## C. 研究結果

図 1 a～d に内リンパ水腫の 1 例を示す。この例の内リンパの体積は 57.4 μL, 外リンパの体積は 101.9 μL であった。内外リンパ体積における内リンパ体積の割合は、34.3%であった。この値は、コントロール耳に比しはるかに 2 倍を超えるものであった。

## D. 考察

我々は、側頭骨連続スライス切片からの撮影を１０スライスに１スライスずつ行った。そのため、全スライスを撮影する方法に比し凸凹が大きかった。このため、スムージングが必要であるが、今後 7 耳すべてにスムージングを行なう予定である。また、今回、我々は、切片の撮影時に基準軸を作成していなかった。この点でもスムージングがより必要になる。ただし、体積の測定には積分を用いるため基準軸の有無は大きな影響を与えないと考えられる。

## E. 結論

側頭骨標本からコンピュータ処理による立体画像は、内外リンパ腔の立体的把握、体積測定、コントロール耳と水腫耳の違いをみるのに有用である。

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なし

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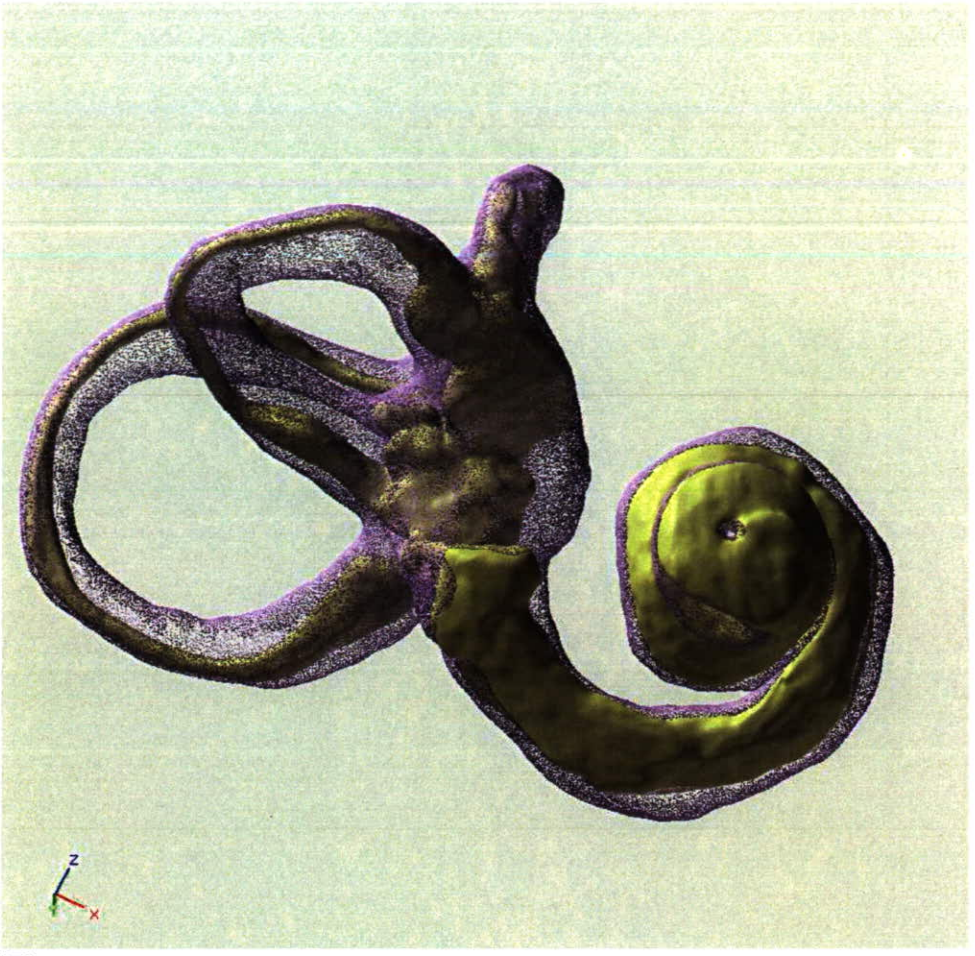


図 1 a

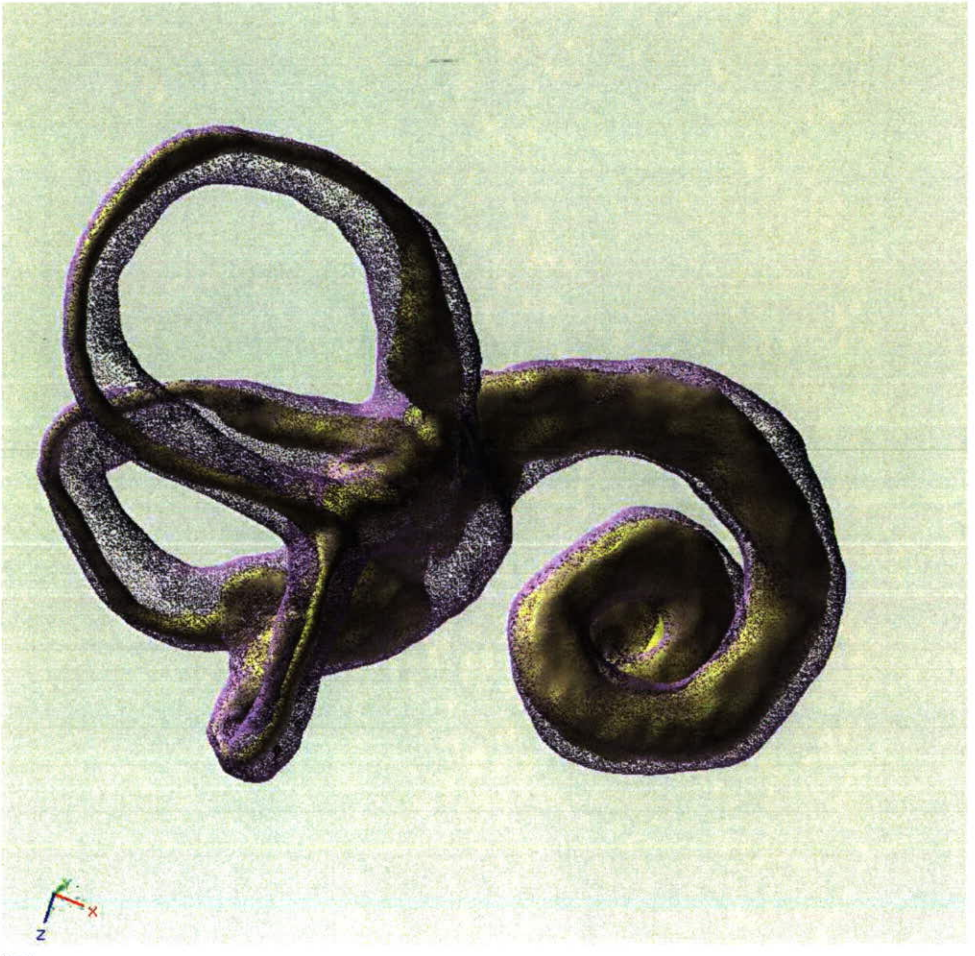


図 1 b

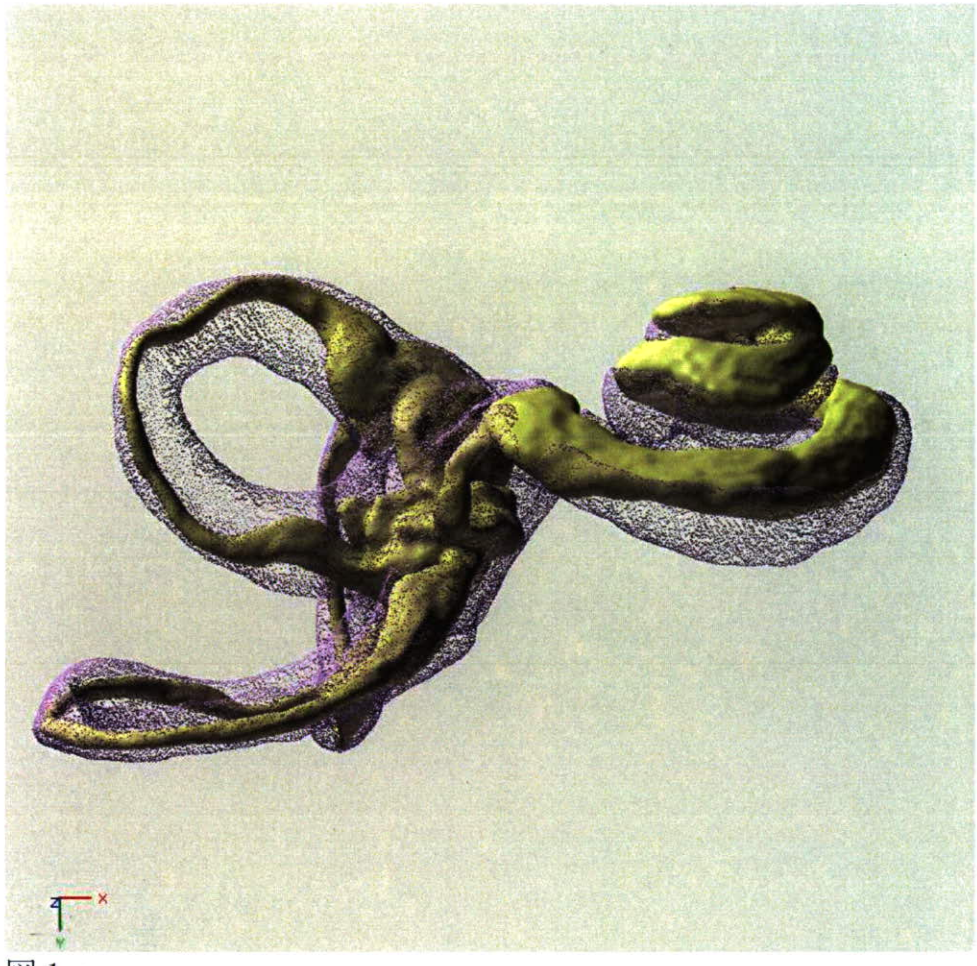

図１ c

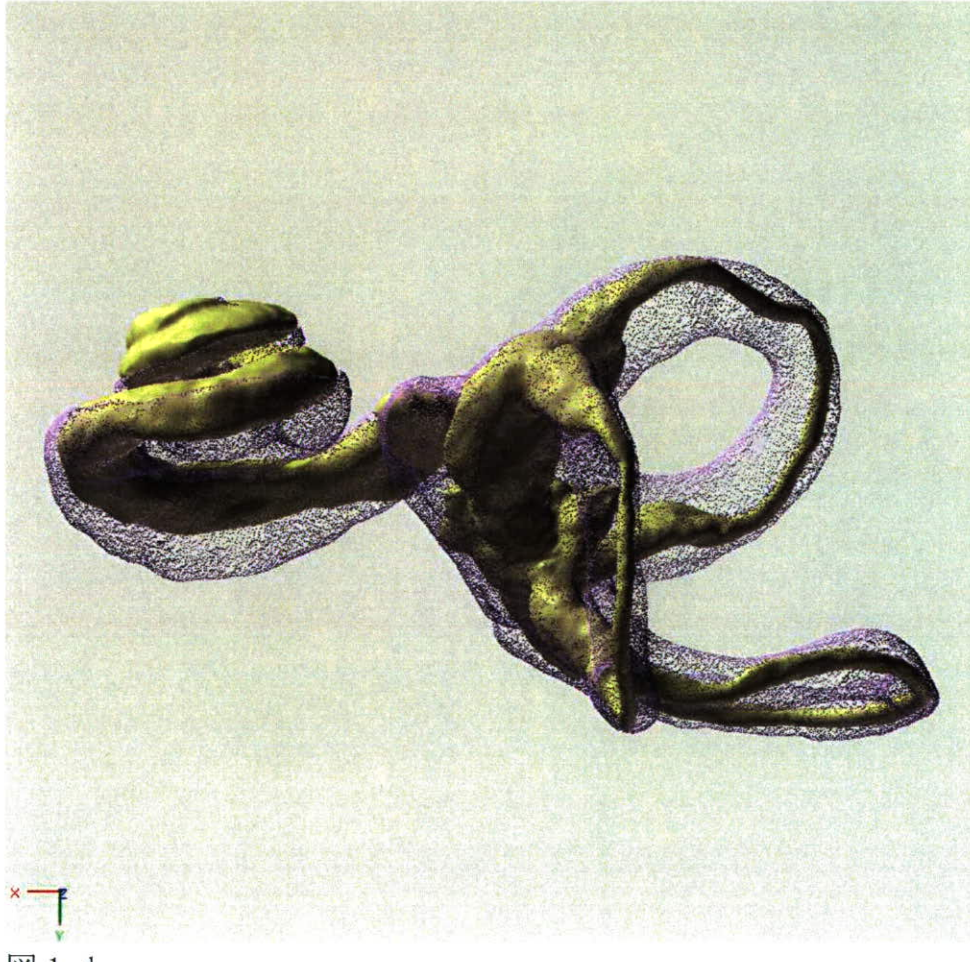

図１ d

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*The Laryngoscope*
Lippincott Williams & Wilkins, Inc.


# Visualization of Endolymphatic Hydrops in Patients With Meniere's Disease

Tsutomu Nakashima, MD; Shinji Naganawa, MD; Makoto Sugiura, MD; Masaaki Teranishi, MD; Michihiko Sone, MD; Hideo Hayashi, MD; Seiichi Nakata, MD; Naomi Katayama, PhD; Ieda Maria Ishida

***Objective:*** **Recently, there have been many reports of intratympanic gentamicin therapy for the treatment of intractable Meniere's disease. Intratympanic administration of steroids has also been used to treat sudden sensorineural hearing loss. We attempted to visualize how the intratympanically administered drug enters the inner ear.** ***Methods:*** **Gadolinium hydrate diluted eightfold with saline was injected intratympanically through the tympanic membrane using a 23 G needle in nine patients with inner ear diseases. With a 3 Tesla magnetic resonance imaging (MRI) unit, three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) imaging was performed.** ***Results:*** **3D-FLAIR MRI clearly revealed that the gadolinium entered the perilymphatic space and delineated the perilymphatic and endolymphatic spaces of the inner ear. In patients with endolymphatic hydrops, the perilymphatic space surrounding the endolymph was small or had disappeared. Gadolinium appeared first in the scala tympani of the basal turn of the cochlea and the perilymphatic space of the vestibule. One day after the intratympanic injection of gadolinium, the gadolinium was observed in almost all parts of the perilymph. Six days after the intratympanic injection, the gadolinium had almost disappeared from the inner ear.** ***Conclusion:*** **We reported the first visualization of endolymphatic hydrops in patients with Meniere's disease. The relationship between the image of the endolymphatic space and functional tests, such as electrocochleography and vestibular-evoked myogenic potential, must be examined in the near future. It is important for the development of intratympanic drug therapies for inner-ear diseases to investigate how the drugs enter and leave the inner ear.** ***Key Words:*** **Endolymphatic hydrops, Meniere's disease, sudden deafness, electrocochleography, vestibular evoked myogenic potential, gadolinium, FLAIR MRI.**

***Laryngoscope,*** **117:●●●–●●●, 2007**

## INTRODUCTION

Although image diagnosis of endolymphatic hydrops may be a key to understanding inner-ear diseases such as Meniere's disease or fluctuating sensorineural hearing loss (HL), imaging the endolymphatic hydrops has not been achieved, except for temporal bone histopathologic specimens in autopsy cases. The composition of the endolymph, with its high potassium and low sodium concentrations, resembles that of the cytosol, in contrast with the composition of the perilymph, which is closer to that of the extracellular medium, with low potassium and high sodium concentrations. However, imaging the endolymphatic space has not been achieved clinically despite these differences in chemical composition. Reissner's membrane, which borders the endolymph and perilymph, is too thin to be visualized.

Electrocochleography (EcochG) and vestibular-evoked myogenic potential (VEMP) have been used to estimate endolymphatic hydrops functionally. The former evaluates the cochlea,[1] and the latter evaluates the vestibule.[2] Endolymphatic hydrops may occur locally or throughout the entire inner ear. It may also fluctuate with the severity of HL or vertigo attacks. One theory for the cause of vertigo attacks in Meniere's disease is the rupture of the extended Reissner's membrane,[3] but the relationship between vertigo attacks and endolymphatic hydrops is not clear. If imaging endolymphatic hydrops becomes possible, a comparison of the images and functional examinations will clarify the significance of the functional examination.

Recently, there have been many reports of intratympanic gentamicin therapy for the treatment of intractable Meniere's disease.[4,5] Intratympanic administration of steroids has also been used to treat sudden sensorineural HL.[6,7] These intratympanic drug therapies are based on the passage of the intratympanically administered drug into the inner ear through the round window membrane. However, in some patients, the passage of the drug through the round window membrane is extremely poor because of connective tissue or granulation tissue over the

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round window.[8] We examined the passage of gadolinium through the round window after its intratympanic administration using magnetic resonance imaging (MRI). The gadolinium entered the perilymphatic space and delineated the perilymphatic and endolymphatic spaces. In patients with Meniere's disease, the extension of the endolymphatic space, called endolymphatic hydrops, could be observed. To our knowledge, this is the first report of the clinical imaging of endolymphatic hydrops.

## METHODS

### *Patients*

Nine patients were enrolled in this study. Age, sex, diagnosis, affected side, average hearing level at 500 Hz, 1 kHz, and 2 kHz, presence or absence of vertigo, and the interval between the intratympanic gadolinium injection and MRI are presented in Table I. Four patients had Meniere's disease, four patients had sudden deafness, and one patient had acute low-tone sensorineural HL. The diagnosis of each disease was made according to the criteria described in the literature.[9–11] However, patient no. 4 had nonrotatory episodic vertigo with fluctuating HL. Six patients first underwent MRI 1 or 2 hours after the intratympanic injection of gadolinium. In three patients, the first MRI was taken 1 day after the intratympanic injection, as shown in Table I. Additional MRIs were taken 6 days after the intratympanic injection in three patients (patients no. 4, 6, and 7 in Table I).

In the patients with Meniere's disease, conservative therapy had failed to control their vertigo attacks, and intratympanic gentamicin therapy was tried. In the patients with acute low-tone sensorineural HL and sudden sensorineural HL, hearing recovery was poor after ordinary treatments, so intratympanic injection of steroids was tried. After our evaluation of the intratympanic injection of gadolinium, we planned intratympanic drug therapies.

The protocol of the study was approved by the Ethics Review Committee of Nagoya University School of Medicine (approval numbers 369, 369–2). All patients gave their informed consent to participation in this study. Their written informed consent was attached to the electronic medical record after permission was given by the patient, in accordance with the suggestion of the Ethics Review Committee.

### *Intratympanic Gadolinium Injection*

Gadodiamide hydrate (Omniscan, Daiich Pharmaceutical Co. Ltd, Tokyo, Japan) was diluted eightfold with saline (v/v 1:7). The diluted gadodiamide hydrate was injected intratympanically through the tympanic membrane using a 23 G needle and a 1 mL syringe after the patient was placed in the supine position with his/her head turned approximately 30° away from the sagittal line toward the healthy ear. The gadolinium was injected until a backflow of fluid into the external ear was observed under a microscope. The amount of diluted gadolinium injected was 0.4 to 0.5 mL. After the injection, the patient remained in the supine position for 60 minutes with his/her head turned approximately 60° away from the sagittal line toward the healthy ear.

### *MRI*

MRI scans were performed with a 3 Tesla MR unit (Trio, Siemens, Erlangen, Germany) using a receive-only eight-channel phased-array coil, as described previously.[12,13] T1-weighted three-dimensional (3D) fast low-angle shot imaging, heavily T2-weighted 3D constructive interference in the steady state imaging, and 3D fluid-attenuated inversion recovery (FLAIR) imaging were performed. For this study, we performed the second 3D-FLAIR with higher in-plane spatial resolution in addition to methods described previously.[12,13] The scan parameters for the second 3D-FLAIR sequence were as follows: repetition time of 9,000 ms, effective echo time of 128 ms, inversion time of 2,500 ms, constant flip angle echo train with flip angle of 180 degrees for conventional turbo spin echo refocusing echo train, echo train length of 23, matrix size of 384 × 384, 12 axial 2 mm thick slices to cover the labyrinth with a 16 cm square field of view, acceleration factor of two using the parallel imaging technique, generalized autocalibrating partially parallel acquisitions. Voxel size was 0.4 mm × 0.4 mm × 2 mm. The number of excitations was one, and the scan time was 15 minutes.

All MRIs were attached to the electronic medical record and reviewed independently on a liquid crystal display in the Department of Radiology and the Department of Otorhinolaryngology. If there were any discrepancies between the interpretations of the two departments, a consensus was reached by discussion.

TABLE I.
Gadolinium Distribution in Inner Ear After Intratympanic Injection.

| | | | | | | | Gadolinium Distribution | | |
|---|---|---|---|---|---|---|---|---|---|
| Patient No. | Age, Sex | Diagnosis | Side | HL | Vertigo | MRI | Cochlea | Vestibule | Semicircular Canals |
| 1 | 57, M | SD | Left | 27 | No | 2 hr | Basal | Whole | Partial |
| | | | | | | 7 hr | Basal, part of 2nd | Whole | Whole |
| 2 | 23, M | ALSNHL | Left | 12 | No | 2 hr | Basal | Whole | Partial |
| 3 | 74, F | SD | Left | 85 | No | 2 hr | Basal | Whole | Partial |
| 4 | 53, M | Meniere's | Left | 35 | Yes | 2 hr | Basal | Whole | Partial |
| 5 | 46, M | Meniere's | Left | 60 | Yes | 2 hr | Basal | Faint | No |
| | | | | | | 1 day | Basal, 2nd | Faint | Faint |
| 6 | 24, F | SD | Right | 68 | Yes | 1 day | Basal, 2nd | Whole | Whole |
| 7 | 55, F | Meniere's | Left | 58 | Yes | 1 day | Basal, 2nd, apical | Whole | Whole |
| 8 | 47, M | SD | Right | 97 | Yes | 1 hr | Basal | Whole | Partial |
| | | | | | | 1 day | Basal, 2nd, apical | Whole | Whole |
| 9 | 65, F | Meniere's | Left | 63 | Yes | 1 day | Basal, 2nd | Faint | Faint |

SD = sudden deafness; ALSNHL = acute low-tone sensorineural hearing loss; HL = average of hearing level of 500 Hz, 1 kHz, and 2 kHz (dB); MRI = period between intratympanic gadolinium injection and magnetic resonance imaging; gadolinium distribution, "whole" = gadolinium was observed wholly in vestibule or semicircular canals.

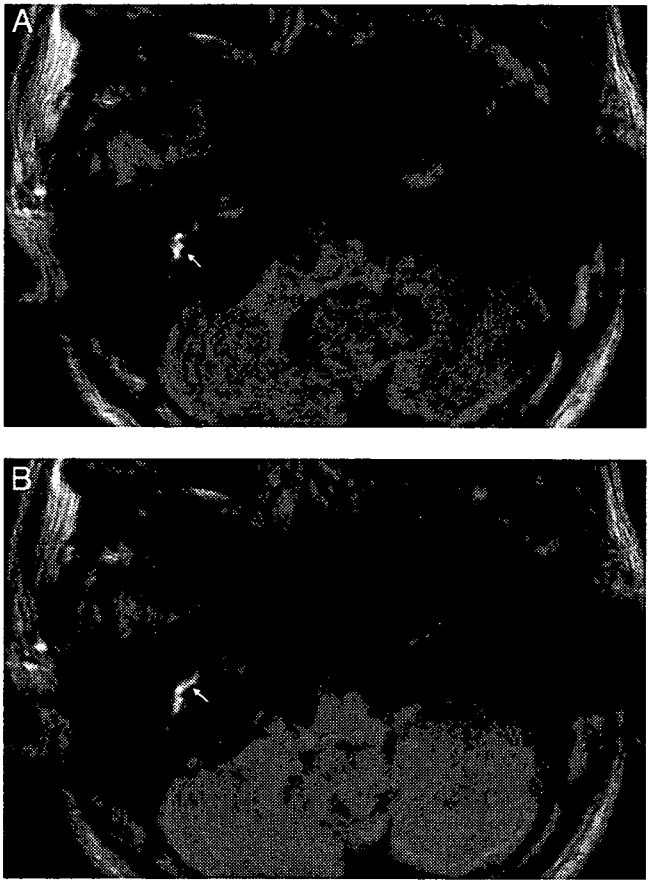


Fig. 1. Three-dimensional fluid-attenuated inversion recovery magnetic resonance images taken 1 hour after intratympanic injection of gadolinium (patient no. 8 in Table I). (A) Gadolinium in vestibule and part of horizontal semicircular canal. Black circle revealed by an arrow in vestibule is crus membranaceum commune. (B) Gadolinium in scala tympani of basal turn of cochlea and vestibule. Arrow indicates scala tympani of basal turn in cochlea.

### *EcochG*

A silver ball electrode was placed on the posteroinferior quadrant of the external ear canal, close to the tympanic membrane. Before the electrode was placed, the skin of the electrode area was cleaned with skin preparation gel for bioelectrical measurements (Skin Pure, Nihonkoden, Tokyo, Japan), and then electrode paste (Biotach, GE Yokogawa Medical, Tokyo, Japan) was spread over the skin area. EcochG was performed while the patient was lying down in a sound-attenuated room. The reference electrode was close to the earlobe, and the ground electrode was on the forehead. The click stimuli were presented four times a second with rarefaction and condensation polarity (Synax 2100, NEC Medical Systems, Tokyo, Japan). The signal was added 500 times through the bandpass filter (100–3,000 Hz). The summating potential (SP) to action potential (AP) ratio was calculated when SP and AP were clear.

### *VEMP*

Surface myogenic potentials in the sternocleidomastoid muscle were added 150 times with a reference electrode over the sternum while clicks (105 dB) were presented to the ipsilateral ear and white noise (75 dB) was presented to the contralateral ear (Synax 2100, NEC Medical Systems, Tokyo, Japan). The ground electrode was on the forehead. The stimulation rate of the clicks was 5 Hz, and the electromyogenic signal was amplified through a bandpass filter (20–2,000 Hz). The patient was instructed to turn his/her head toward the contralateral side in the sitting position to activate the sternomastoid muscle.

## RESULTS

On MRIs taken 1 or 2 hours after the intratympanic injection of gadolinium, the gadolinium was observed in the vestibule, parts of the lateral semicircular canals close to the vestibule, and the scala tympani of the basal turn of the cochlea (Fig. 1). The gadolinium that entered the scala tympani of the cochlea through the round window membrane moved quickly into the vestibule. When the gadolinium entered the perilymph of the vestibule, the endolymphatic space without gadolinium could be seen, as shown in Figure 1A. The utricle and crus membranaceum commune, which is located at the meeting point of anterior and posterior semicircular canal crura, could be seen relatively clearly. However, the saccule, which is smaller than the utricle, was not as clearly visible as the utricle. One day after the intratympanic injection of gadolinium, the gadolinium had infiltrated a wider area in the semicircular canals and the cochlea. These results are summarized in Table I. Figure 2 shows the gadolinium inside the

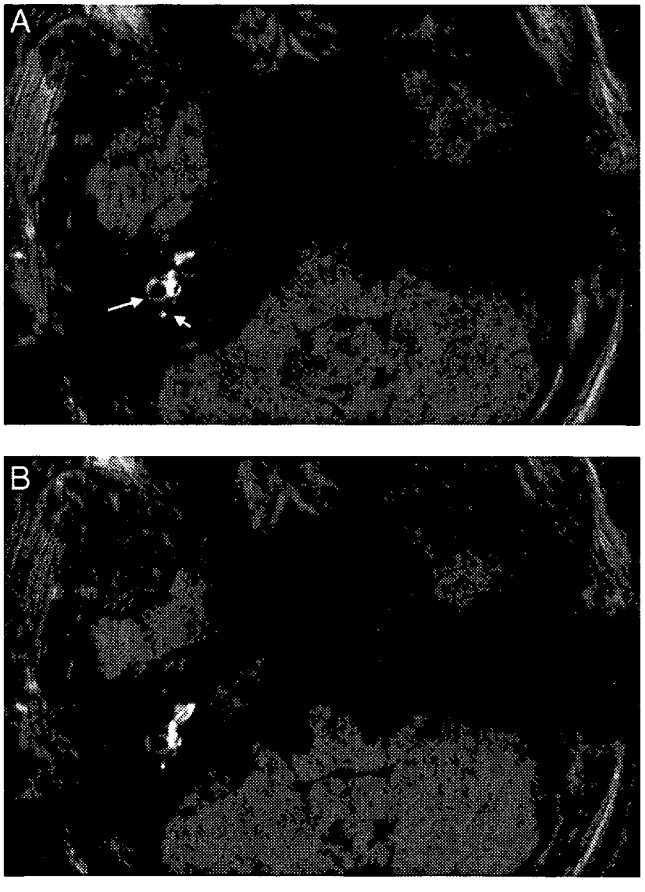


Fig. 2. Three-dimensional fluid-attenuated inversion recovery magnetic resonance images taken 1 day after intratympanic injection of gadolinium (patient no. 8 in Table I). (A) Gadolinium in second and apical turns of cochlea, vestibule, and semicircular canals. Long arrow indicates horizontal semicircular canal and short arrow posterior semicircular canal. (B) Gadolinium in basal and second turns of the cochlea, vestibule, and semicircular canals.

Fig. 3. Three-dimensional fluid-attenuated inversion recovery magnetic resonance image taken 1 day after intratympanic injection of gadolinium (patient no. 5 in Table I). Black areas indicated by arrows are surrounded by gadolinium-filled perilymph. Endolymphatic hydrops in basal turn of cochlea is clearly shown. Gadolinium in vestibule and semicircular canals is faintly visible.

inner ear 1 day after the intratympanic injection of gadolinium. In Figure 2, the border between the perilymph and endolymph inside the vestibule is visible, as it was on the MRI taken 1 hour after the intratympanic injection of gadolinium. This means that the entrance of the gadolinium into the endolymph from the perilymph was negligible in the vestibule on the first day. However, the gadolinium moved toward upper turns of the cochlea during this period, and the scala vestibuli and scala media became visible (Fig. 2).

In patients no. 5 and 9, who had Meniere's disease, gadolinium was barely visible in the vestibule because endolymphatic hydrops occupied the perilymphatic space. In patient no. 5, the gadolinium was only faintly visible in the vestibule 1 day after the intratympanic injection of gadolinium, similarly 2 hours after the intratympanic injection. In the cochlea, the gadolinium moved toward the upper turn, and the endolymphatic hydrops inside the perilymphatic space filled with the gadolinium was observed in the basal turn of the cochlea (Fig. 3). It is clear that the endolymphatic space in Figure 3 is significantly enlarged compared with that in Figure 2. In Figure 3, the gadolinium does not reach the helicotrema. Accordingly, the gadolinium appeared in the scala vestibule of the basal turn by way of the lateral wall of the cochlea not by way of the helicotrema. In patient no. 5, VEMP was absent, and the SP/AP ratio on EcochG was high (48%). This patient had frequent drop attacks despite the disappearance of rotatory vertigo after earlier intratympanic gentamicin therapy. In patient no. 9, endolymphatic hydrops was also observed in the cochlea in the MRI taken 1 day after the intratympanic gadolinium injection. In patient no. 9, VEMP was absent, and AP in EcochG could not be obtained clearly. This patient had rotatory vertigo attacks even after intratympanic gentamicin therapy.

One day after the intratympanic injection of gadolinium, the gadolinium-filled perilymphatic space was small in the vestibule of patient no. 7, who had Meniere's disease, because of vestibular endolymphatic hydrops (Fig. 4A). It is clear that the endolymphatic space in the vestibule in Figure 4A is larger than that in Figure 2A. In this patient, each cochlear turn was visualized separately because almost all gadolinium was observed only in the scala tympani in the cochlea (Fig. 4B). It appears that gadolinium that passes through the helicotrema or the lateral wall toward the scala vestibuli was blocked by the extended endolymphatic hydrops in the cochlea. This patient had an extremely high SP/AP ratio (100%) without VEMP.

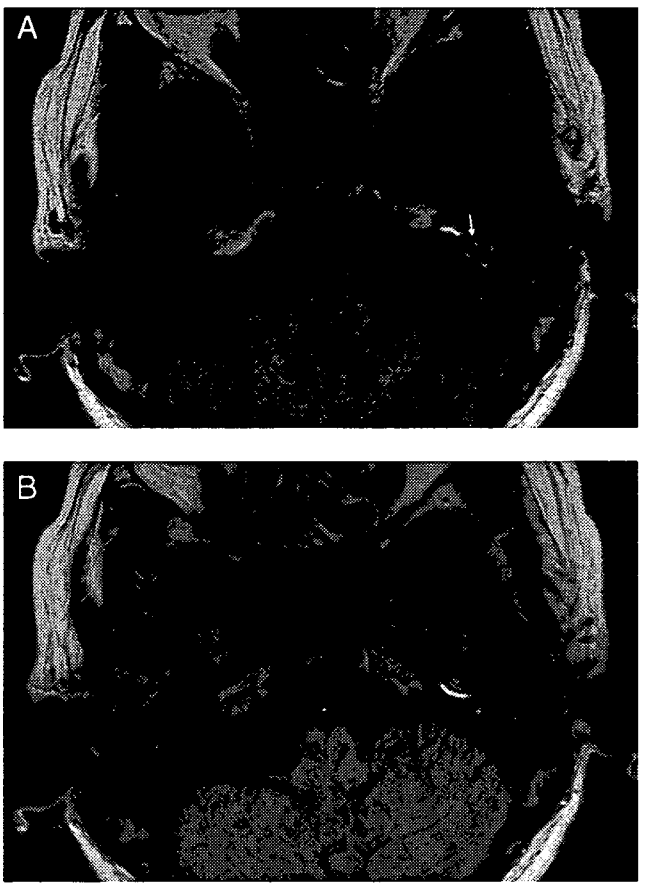


Fig. 4. Three-dimensional fluid-attenuated inversion recovery magnetic resonance images taken 1 day after intratympanic injection of gadolinium (patient no. 7 in Table I). (A) Gadolinium in basal and second turns of cochlea, vestibule, and semicircular canals. Large black areas in vestibule represent vestibular endolymphatic hydrops (indicated by arrow). (B) Gadolinium in three turns of cochlea. Almost all gadolinium was present in scala tympani of cochlea.

VEMP was present in six patients, except patients no. 5, 7, and 9. The amplitude ratio of the VEMP on the affected side to that on the healthy side was more than 75% in these six patients. No high SP/AP ratios on EcochG were observed except for patients no. 5 and 7, although EcochG was not performed in patients no. 2 or 3. The SP/AP ratio could not be obtained because of low AP amplitude in patients no. 6, 8, and 9.

Six days after the intratympanic injection of gadolinium, MRI was performed in three patients (no. 4, 6, and 7 in Table I). At this time, the gadolinium had almost dis-

appeared from the inner ear. However, there was interpatient variability in the pattern of gadolinium disappearance. In one patient with Meniere's disease (patient no. 4), the residual gadolinium was visible compared with that in the other two patients.

No adverse effects of the intratympanic injection of gadolinium were observed. There was also no change in tinnitus.

## DISCUSSION

Gadolinium was not visible in the tympanic cavity 1 hour after the transtympanic injection. Gadolinium in the tympanic cavity might have quickly disappeared through the auditory tube. The movement of the gadolinium in the middle ear needs to be studied further after investigation of suitable gadolinium concentration for 3D-FLAIR MRI.

Because intratympanically administered contrast enhancement material moves first into the perilymphatic space of the inner ear, precise MRIs taken soon after intratympanic administration can reveal the border of the endolymph and perilymph. Therefore, we could visualize endolymphatic hydrops in humans. In an MRI taken 1 day after the intratympanic injection of gadolinium, the border of the perilymph and endolymph was clearly visible, and the gadolinium was observed almost wholly inside the inner ear. Therefore, we consider that MRI undertaken 1 day after the intratympanic injection of gadolinium provides maximum information to observe endolymphatic hydrops both in the cochlea and vestibule.

Using 1.5 Tesla T1 MRI, Zou et al.[14] have previously shown that intratympanically administered gadolinium moved into the inner ears of two patients. Our study with 3 Tesla 3D-FLAIR MRI provided very clear images and made possible the visualization of endolymphatic hydrops, although the concentration of the gadolinium injected into the tympanic cavity was one eighth that of the original gadolinium solution. Our T1 MRIs taken at 3 Tesla revealed the distribution of gadolinium in the inner ear. However, the border of the endolymph and perilymph was markedly clearer on 3D-FLAIR MRI than on T1 MRI. FLAIR sequences sometimes demonstrate hemorrhage or a high concentration of protein, which are difficult to detect with T1- or T2-weighted MRI.[12,13] Two-dimensional (2D)-FLAIR sequences show flow-related artifacts caused by the inflow of cerebrospinal fluid (CSF) from outside the slice volume, which sometimes obscures the pathology. We have reported previously that CSF-related flow artifacts are significantly reduced on 3D-FLAIR images relative to those on 2D-FLAIR images.[15] The 3D-FLAIR sequence allows the detection on serial, thin slices of conditions that mimic other pathologies of the inner ear, such as inner-ear hemorrhage or high concentrations of protein.[13]

In three patients with Meniere's disease without VEMP, the movement of gadolinium into the vestibule was restricted. It is assumed that the extremely large endolymphatic hydrops in the vestibule prevented the movement of the gadolinium from the scala tympani of the cochlea to the vestibule. A decrease in or disappearance of VEMP, which is a function of the saccule, is associated with endolymphatic hydrops in the vestibule.[2] The relationship between the image of the endolymphatic space and functional tests, such as EcochG and VEMP, must be examined further in the near future.

After 6 days from the intratympanic injection of gadolinium, the gadolinium had almost disappeared from the inner ear. However, there was interpatient variability in the pattern of gadolinium disappearance. The pattern or speed of the disappearance may be associated with circulation of the inner ear. It is important for the development of intratympanic drug therapies for inner-ear diseases to investigate how the drugs enter and leave the inner ear.

## CONCLUSIONS

1. Intratympanically administered gadolinium moves quickly into the scala tympani of the basal turn of the cochlea and the perilymphatic space of the vestibule. One day after the intratympanic administration, the gadolinium appears in almost all parts of the perilymph inside the inner ear.
2. With use of 3 Tesla 3D-FLAIR MRI, the size of endolymphatic space can be evaluated clearly after the intratympanic gadolinium administration.
3. Extremely large endolymphatic hydrops in the vestibule may prevent the intratympanically administered drug from moving into the vestibule and semicircular canals. This should be taken into consideration for intratympanic gentamicin therapy in patients with Meniere's disease.

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TECHNICAL NOTE

# Imaging of Endolymphatic and Perilymphatic Fluid at 3T After Intratympanic Administration of Gadolinium-Diethylene-Triamine Pentaacetic Acid

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M. Kawamura
H. Fukatsu
M. Sone
T. Nakashima

**SUMMARY:** By optimizing the inversion time of a 3D inversion-recovery turbo spin-echo sequence at 3T, we obtained separate images of endolymphatic and perilymphatic space 24 hours after intratympanic administration of gadolinium contrast material. In patients with Ménière disease, endolymphatic hydrops were detected not only in the cochlea but also in the vestibule. Fusion of the 2 types of images visualized the entire fluid space of the labyrinth and the spatial relationship of the 2 spaces.

After intratympanic injection of gadolinium-diethylene-triamine pentaacetic acid (Gd-DTPA) in an animal study, Gd-DTPA was absorbed through the round window membrane and was distributed mainly into the perilymphatic space of the labyrinth.[1] Enlarged endolymphatic space in patients with Ménière disease has been successfully recognized as an area with low signal intensity partly surrounded by high-signal intensity perilymphatic fluid on 3D-fluid-attenuated inversion recovery (FLAIR) images obtained after intratympanic injection of Gd-DTPA.[2] However, the boundary between the cochlear endolymphatic space and surrounding bone was not clear, as both had low signal intensity on 3D-FLAIR images. To visualize endolymphatic space in the labyrinth as high signal intensity, while maintaining the differentiation from perilymphatic fluid space, we selected an inversion time shorter than that of 3D-FLAIR to suppress the signal intensity of perilymphatic fluid with a higher concentration of Gd-DTPA.

## Materials and Methods

### *Patients*

A total of 4 patients (3 with clinically diagnosed Ménière disease and 1 with sudden sensorineural hearing loss, ages 38–69 years; 2 men and 2 women) underwent intratympanic administration of Gd-DTPA bis-methylamide (Gd-DTPA-BMA, Omniscan; Daiichi Pharmaceutical, Tokyo, Japan). These patients were scheduled for intratympanic injection therapy with gentamicin (for the 3 patients with Ménière disease) or with a steroid (for the patient with sudden sensorineural hearing loss). We obtained written informed consent from all patients. The institutional review board of our university hospital approved our study.

### *Intratympanic Gadolinium Injection*

The detailed methods for intratympanic gadolinium injection have been reported previously.[2] According to the results from this previous study, scan delay after intratympanic gadolinium injection was determined as 24 hours to allow the distribution of gadolinium widely in the perilymphatic space of the labyrinth.

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Gd-DTPA-BMA was diluted eightfold with saline (v/v 1:7). We injected the diluted Gd-DTPA-BMA intratympanically through the tympanic membrane using a 23-gauge needle and a 1-mL syringe after the patient was placed in the supine position with their head turned approximately 30° away from the sagittal line toward the healthy ear. The diluted Gd-DTPA-BMA was injected until a backflow of fluid into the external ear was observed through a microscope, resulting in an injected volume of 0.4 to 0.5 mL per patient. After the injection, the patients remained in the supine position for 60 minutes with the head turned approximately 60° away from the sagittal line toward the healthy ear.

### *MR Imaging*

We performed all scans on a 3T MR imaging scanner (Magnetom Trio; Siemens, Erlangen, Germany) using a receive-only 12-channel phased-array coil. T1-weighted 3D-fast low-angle shot (FLASH) and conventional 3D-FLAIR imaging were acquired 24 hours after intratympanic injection of diluted Gd-DTPA-BMA. In addition, T2-weighted 3D-constructive interference in the steady state (CISS) imaging was performed to obtain reference images of labyrinthine fluid-space anatomy.

The parameters for 3D-FLASH were as follows: TR, 4.3 ms; TE, 1.97 ms; flip angle, 10° with radio frequency spoiling; matrix size, 256 × 256; and 96 axial 0.8-mm-thick sections covering the posterior fossa with a 16-cm square FOV. The NEX was 2, giving a total scan time of 2 minutes 51 seconds.

The parameters for 3D-CISS were as follows: TR, 11.42 ms, TE, 5.71 ms; flip angle, 50°; matrix size, 320 × 320; and 48 axial 0.8-mm-thick sections with a 16-cm square FOV. The NEX was 1, and the scan time was 3 minutes 42 seconds.

The parameters for 3D-FLAIR were as follows: TR, 9000 ms; TE, 128 ms; flip angle, 180° (constant) for the turbo spin-echo refocusing echo-train; echo-train length, 23; matrix size, 384 × 384; and 12 axial 2-mm-thick sections covering the labyrinth with a 16-cm square FOV acquired with use of the generalized autocalibrating partially parallel acquisition parallel imaging technique with an acceleration factor of 2.[3] The NEX was 1, and the scan time was 14 minutes.

In the first 2 patients, 2D inversion-recovery (IR) turbo spin-echo imaging with TR, TE, and echo-train length identical to those of the 3D-FLAIR protocol was performed with various inversion times (2300, 2100, 1900, 1700, 1500, 1300, 1100, 900, 700, and 500 ms) to determine the null point of perilymphatic fluid containing a low concentration of Gd-DTPA-BMA at 24 hours after intratympanic injection. In both patients, 2D-IR with inversion times of 900 and 1100 ms

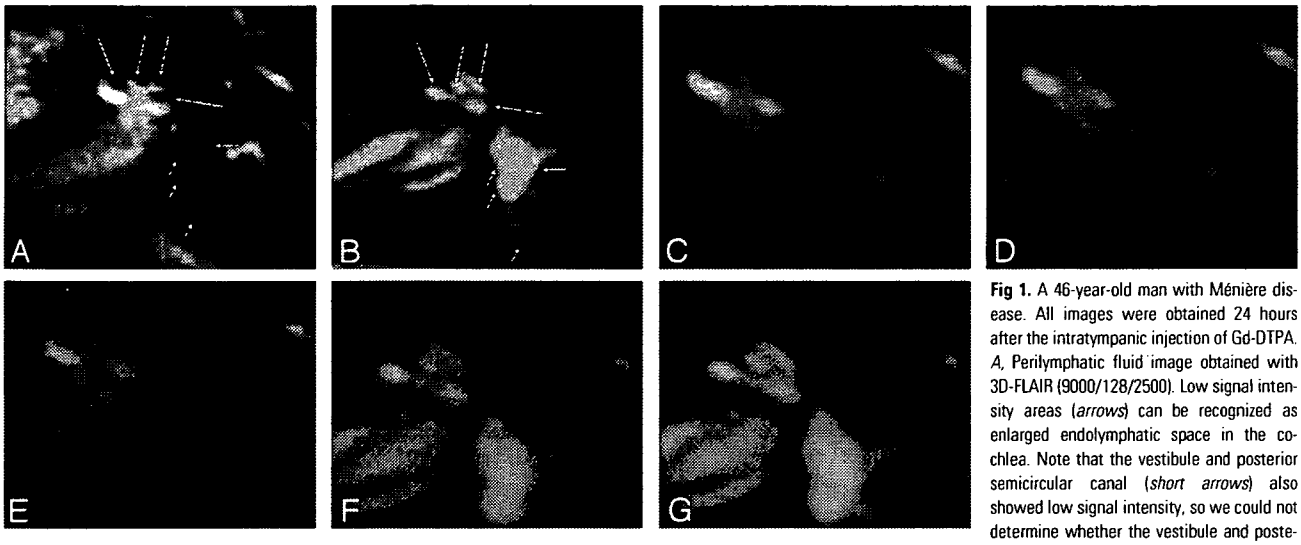


**Fig 1.** A 46-year-old man with Ménière disease. All images were obtained 24 hours after the intratympanic injection of Gd-DTPA. *A,* Perilymphatic fluid image obtained with 3D-FLAIR (9000/128/2500). Low signal intensity areas (*arrows*) can be recognized as enlarged endolymphatic space in the cochlea. Note that the vestibule and posterior semicircular canal (*short arrows*) also showed low signal intensity, so we could not determine whether the vestibule and posterior semicircular canal were filled with endolymphatic fluid. *B,* Endolymphatic fluid image obtained with a 3D inversion-recovery sequence (9000/128/1000). Endolymphatic space in the cochlea (*arrows*) shows high signal intensity on this image. This image confirmed that the vestibule and posterior semicircular canal were filled with fluid. *C–G,* Fusion of a perilymphatic fluid image (*C*) and an endolymphatic fluid image (*G*) with transitional images (*D–F*). By changing the fusion mixture rate on a workstation, the spatial relationship between perilymphatic and endolymphatic space was easily appreciated in both the cochlea and vestibule. In this case, endolymphatic space was enlarged in both the cochlea and vestibule, but the enlargement was especially prominent in the vestibule. Note that CSF in the internal auditory canal is visualized as high signal intensity on the endolymphatic fluid image (*G*). The signal intensity of perilymphatic space is just suppressed. Thus, the term *endolymphatic image* is only useful for labyrinthine space.

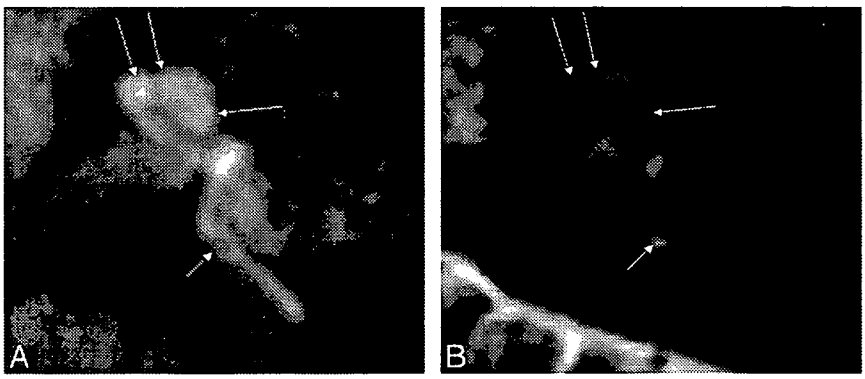


**Fig 2.** A 43-year-old woman with sudden sensorineural hearing loss in the left ear. All images were obtained 24 hours after the intratympanic injection of Gd-DTPA. *A,* Perilymphatic fluid image obtained with 3D-FLAIR (9000/128/2500). Areas of low signal intensity in the position of the cochlear duct (*arrows*) cannot be recognized as the endolymphatic space in the cochlea, probably because of their small size. Note that the endolymphatic space of the posterior ampulla (*short arrow*) showed low signal intensity. *B,* Endolymphatic fluid image obtained with a 3D inversion-recovery sequence (9000/128/1000). The endolymphatic space in the cochlea (*arrows*) cannot be recognized as high signal intensity on this image. Note that the endolymphatic space of the posterior ampulla (*short arrow*) showed high signal intensity alternatively compared with Fig 2*A*.

showed the lowest signal intensity in the perilymphatic space. Thus, in all 4 subjects, an inversion time of 1000 ms was selected for 3D-IR imaging of endolymphatic space. Other 3D-IR parameters for endolymphatic imaging were identical to those of 3D-FLAIR. If the size of the endolymphatic space was enlarged, endolymphatic and perilymphatic images were reviewed while referring to 3D-CISS images. The cochlear endolymphatic space is thought to be enlarged if the cochlear duct (endolymphatic space in the cochlea) is bulging toward the perilymphatic space in the scala vestibuli. Also, the vestibular endolymphatic space is thought to be enlarged if the endolymphatic space is larger than the perilymphatic space.

### *Image Fusion*

Endolymphatic (3D-IR with an inversion time of 1000 ms) and perilymphatic images (3D-FLAIR) were fused on a Leonardo workstation (Siemens, Erlangen, Germany). To confirm that the spatial relationship between the perilymphatic and endolymphatic images was anatomically correct, we viewed the fused images on the workstation monitor while changing the weighting scale continuously from pure 3D-IR to pure 3D-FLAIR.

## Results

In all patients, an area of low signal intensity in the labyrinth on 3D-FLAIR showed high signal intensity on endolymphatic images (Fig 1*A,B*). By scaling the weighting on a fused image, the spatial relationship between the endolymphatic and perilymphatic images was clearly discernible (Fig 1*C–G*). In the 3 patients with Ménière disease, the endolymphatic space seemed to be enlarged. In the patient with sudden hearing loss, no enlargement of the endolymphatic space was noted (Fig 2).

## Discussion

Many researchers[4] have attempted separate visualization of perilymphatic and endolymphatic fluid space with MR imaging. Direct visualization of the Reissner membrane with use of high spatial-resolution imaging was successful in animals[5] and human cadavers[6,7]; however, clear visualization in a living human subject has not been successful. Four hours after intravenous administration of Gd-DTPA in healthy human volunteers, a slight increase in signal intensity was noted in the labyrinth.[8] However, probably because of a gadolinium concentration that was too low in the perilymphatic space, differentiation between the endolymphatic and perilymphatic space was not achieved. Intratympanic injection of Gd-DTPA and the application of 3D-FLAIR at 3T made the visualization of endolymphatic hydrops possible in vivo.[2] Although intratympanically administered Gd-DTPA distributes mainly into the perilymphatic fluid space and not into the endolymphatic

space, on 3D-FLAIR the hypointense endolymphatic space was difficult to differentiate from the surrounding bone and air. To delineate the endolymphatic space more clearly and to allow the quantification of the endolymphatic-space volume in the future, the endolymphatic space needs to be visually differentiated not only from the perilymphatic space but also from bone and air. By changing the inversion time, it was possible to separately visualize the endolymphatic and perilymphatic spaces as positive signal intensity. This will allow volume quantification of each space in the future if the spatial resolution is improved. Quantification of each space is important for the objective diagnosis of endolymphatic hydrops and for the monitoring of treatment effectiveness.

Fusion techniques convinced us that each space was separately visualized not only in the cochlea, but also in the vestibule and semicircular canals.

In our study, the labyrinth without intratympanic gadolinium injection (the other side ear) showed uniformly high signal intensity of the whole labyrinth on endolymphatic imaging with use of 3D-IR. This means that the suppression of perilymph on endolymphatic imaging by the present method in the injected side is based on the distribution of gadolinium.

One of the limitations of our presented method was the long acquisition time, 30 minutes for 2 kinds of lymphatic space images. One possibility to obtain endolymphatic images in a shorter period of time is the subtraction of perilymphatic-space images from T2-weighted images. This might allow us to obtain endolymphatic-space images if the subject is nearly motionless during the scans.

The other limitation of our method was the potential rupture of Reissner membrane in a very advanced case of Ménière disease. In such case, contamination of the endolymph and perilymph would occur and endolymphatic space might show low signal intensity on endolymphatic imaging.

## Conclusion

By optimizing the inversion time, it was possible to obtain images of the endolymphatic and perilymphatic spaces. The endolymphatic space was differentiated not only from the perilymphatic space, but also from bone and air. This method might open the door to objective evaluation of endolymphatic-space disease.

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# Separate visualization of endolymphatic space, perilymphatic space and bone by a single pulse sequence; 3D-inversion recovery imaging utilizing real reconstruction after intratympanic Gd-DTPA administration at 3 Tesla

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**Abstract** Twenty-four hours after intratympanic administration of gadolinium contrast material (Gd), the Gd was distributed mainly in the perilymphatic space. Three-dimensional FLAIR can differentiate endolymphatic space from perilymphatic space, but not from surrounding bone. The purpose of this study was to evaluate whether 3D inversion-recovery turbo spin echo (3D-IR TSE) with real reconstruction could separate the signals of perilymphatic space (positive value), endolymphatic space (negative value) and bone (near zero) by setting the inversion time between the null point of Gd-containing perilymph fluid and that of the endolymph fluid without Gd. Thirteen patients with clinically suspected endolymphatic hydrops underwent intratympanic Gd injection and were scanned at 3 T. A 3D FLAIR and 3D-IR TSE with real reconstruction were obtained. In all patients, low signal of endolymphatic space in the labyrinth on 3D FLAIR was observed in the anatomically appropriate position, and it showed negative signal on 3D-IR TSE. The low signal area of surrounding bone on 3D FLAIR showed near zero signal on 3D-IR TSE. Gd-containing perilymphatic space showed high signal on 3D-IR TSE. In conclusion, by optimizing the inversion time, endolymphatic space, perilymphatic space and surrounding bone can be separately visualized on a single image using a 3D-IR TSE with real reconstruction.

**Keywords** Inner ear · Endolymphatic hydrops · Magnetic resonance · Meniere's disease

## Introduction

In an animal study, it has been shown that Gd-DTPA absorbed through the round window membrane distributed mainly into perilymphatic space following intratympanic gadolinium-diethylene-triamine pentaacetic acid (Gd-DTPA) injection [1]. Enlarged endolymphatic space in patients with Meniere's disease has been successfully recognized as the area with low signal intensity on 3D fluid-attenuated inversion-recovery (FLAIR) images obtained after intratympanic injection of Gd-DTPA [2]. Enlarged endolymphatic space was partly surrounded by perilymphatic fluid with high signal on 3D-FLAIR images.

Delineation of the boundary between cochlear endolymphatic space and surrounding bone was not clear, as the bone and endolymphatic space showed low signal intensity on 3D-FLAIR images.

To visualize endolymphatic space in the labyrinth as high signal while maintaining the separation from perilymphatic fluid space, a 3D inversion-recovery turbo spin echo sequence (3D-IR TSE) with an inversion time shorter than that of 3D FLAIR (to suppress the signal of perilymph fluid with higher Gd-DTPA concentration) might successfully suppress the signal of perilymph such that only endolymph would have positive signal, allowing the depiction of the border between bone and endolymphatic space.

This method would require the acquisition of two separate sequences to obtain the endolymphatic and perilymphatic anatomy. Mutual anatomical relationships between endo-and perilymphatic space could not be

appreciated without the fusion of two separately obtained images. Instead of this, we assumed that the real reconstruction of inversion recovery data might, with a single sequence, be able to separately visualize endolymph, perilymph and bone in a clinically acceptable scan time. Features of the real reconstruction of inversion recovery data have been reported previously [3–5].

The purpose of this study was to evaluate whether 3D inversion-recovery turbo spin echo (3D-IR-TSE) with real reconstruction could separate the signals of perilymph (positive value), endolymph (negative value) and bone (near zero) by setting the inversion time between the null point of Gd-containing perilymph fluid and that of the endolymph fluid without Gd.

## Materials and methods

### Patients

Thirteen patients with clinically suspected endolymphatic hydrops (nine Meniere's disease, two delayed endolymphatic hydrops [6, 7] and two acute low-tone sensorineural hearing loss, age 24-74 years, mean age 39.5 years, five men and eight women) underwent intratympatic administration of gadolinium-diethylene-triamine pentaacetic acid-bis (methylamide) (Gd-DTPA-BMA; Omniscan, Daiichi Pharmaceutical Co. Ltd., Tokyo, Japan). In two patients with delayed endolymphatic hydrops, intratympanic injection was performed for both the left and right ears. Thus, 15 ears were included in this study. These patients were scheduled for intratympanic injection therapy, with gentamicin to control severe vertigo or with steroid for the treatment of sensorineural hearing loss [8–11].

Clinical diagnosis was based on the patients' history and various otological tests such as audiograms, electrocochleograms and vestibular-evoked myogenic potentials (VEMP).

Written informed consent was obtained from all patients. This study was approved by the institutional review board of our university hospital.

### Intratympanic gadolinium injection

The detailed methods for intratympanic gadolinium injection have been reported previously [2].

Gd-DTPA BMA was diluted eightfold with saline (v/v 1:7). The diluted Gd-DTPA BMA was injected intratympanically through the tympanic membrane using a 23-G needle and a 1-ml syringe after the patient was placed in the supine position with his/her head turned approximately 30° away from the sagittal line toward the other ear. The diluted Gd-DTPA-BMA was injected until a backflow of fluid into the external ear was observed under a microscope. The amount of diluted gadolinium injected was 0.4 to 0.5 ml. After the injection, the patient remained in the supine position for 60 min with his/her head turned approximately 60° away from the sagittal line toward the other ear.

### MR imaging

All scans were performed on a 3-T MRI scanner (MAGNETOM Trio; Siemens Medical Solutions, Erlangen, Germany) using a receive-only 12-channel phased-array coil. Twenty-four hours after intratympanic injection of diluted Gd-DTPA BMA, T1-weighted 3D-FLASH (fast low-angle shot) and conventional 3D-FLAIR (fluid-attenuated inversion recovery) imaging was performed. In addition, T2-weighted 3D-CISS (constructive interference in the steady state) imaging was performed to obtain reference images of labyrinthine fluid-space anatomy.

The parameters for 3D-FLASH were as follows: repetition time (TR) of 4.3 ms, echo time (TE) of 1.97 ms, flip angle of 10 degrees with RF spoiling, matrix size of 256×256, and 96 axial 0.8-mm-thick slices covering the posterior fossa with a 16-cm square field of view. The number of excitations was two, giving a total scan time of 2 min 51 s. The parameters for 3D-CISS were as follows: TR of 11.42 ms, TE of 5.71 ms, flip angle of 50 degrees, matrix size of 320×320, and 48 axial 0.8-mm-thick slices with a 16-cm square field of view. The number of excitations was one, and the scan time was 3 min 42 s.

The parameters for 3D-FLAIR and 3D-IR TSE were as follows: TR of 9,000 ms, TE of 134 ms, flip angle of 180 degrees (constant) for the turbo-spin-echo refocusing echo train, echo train length of 23, matrix size of 384×384, and 12 axial 2-mm-thick slices covering the labyrinth with a 16-cm square field of view, acquired using the GRAPPA parallel imaging technique with an acceleration factor of 2 [12]. The number of excitations was one, and the scan time was 14 min.

In a previous pilot study, a TI of 1,000 ms was selected for 3D inversion-recovery imaging of endolymphatic space, nulling the signal of Gd-containing perilymph. As the suppression of fluid without Gd could be achieved with a TI of 2,500 ms on 3D-FLAIR images, a TI of 1,700 ms (near the midpoint between 1,000 ms and 2,500 ms) was selected to assign positive longitudinal magnetization to perilymphatic fluid, negative longitudinal magnetization to endolymphatic fluid and zero magnetization to compact bone and air.

### Endolymphatic hydrops on MR images

Endolymphatic hydrops was determined subjectively by an experienced neuroradiologist who has 20 years of experience in inner-ear MR imaging using the following criteria: Endolymphatic hydrops in the cochlea is thought to be positive if the negative signal area on 3D-real IR in the cochlear peripheral area is bulging toward the scala vestibuli. Endolymphatic hydrops in the vestibule is thought to be