定し，2ヵ月たてば完全に固定するといってよい．したがって，治療は，発症後，1ヵ月間が勝負ということになる．耳鳴を苦にする症例も多いが，聴力の経過がよい症例では，耳鳴も軽快していく．

薬物療法として全国調査の結果から，ステロイドが85％の症例に用いられている．このほか，循環障害の改善を目的にプロスタグランディンが33％の症例に，循環・代謝改善を目的にATPが87％の症例に用いられている．治療効果が乏しい症例では，高気圧酸素療法や星状神経節ブロックを行っている施設もある．

6. なぜ局所治療か

内耳血流量は，心拍出量に比べてきわめて小さい．モルモットで心拍出量の1万分の1程度，ウサギで10万分の1程度であり，人では，百万分の1程度といわれている．このように，全身の血流量と比較するとおどろくほど少ない．したがって，全身投与ではなく，局所的に薬剤を内耳に投与し，内耳への薬剤移行量を格段に上げようとするものである．一般的な治療としてステロイドの全身投与が行われているが，糖尿病患者では，ステロイドが使いにくいことも局所療法が注目されている理由である．

突発性難聴に対する局所療法の文献的報告は，ほとんどが21世紀になってから出てきている．緑内障など眼科の疾患に目薬が広く用いられているが，内耳疾患においてもようやく局所療法が広まりつつある．

7. 局所療法の一般的な方法

ステロイド(デキサメタゾンかメチルプレドニゾロン)を1mL注射器と長針を用いて鼓膜経由に鼓室内に注入する．注入できる量は，だいたい0.5mL程度までである．鼓室内の薬剤は，薄い蝸牛窓(正円窓)を通って内耳に入っていくが，できるだけ内耳に入りやすくするために，注入後，30分間，注入した耳を上にして臥位を保つ．このような内耳への薬剤投与法は，保存的治療に抵抗するメニエール病に対するゲンタマイシン鼓室内注入療法と同様である．

図1は，8倍に薄めたガドリニウム造影剤を鼓室内に注入し，1日たって撮ったMRIである．注入側内耳全体(正確には内耳の外リンパ腔)に薬剤がよく分布しているのがわかる．注意すべきは，蝸牛窓の透過性が，まったくないか相当悪い人が1割程度いることである．

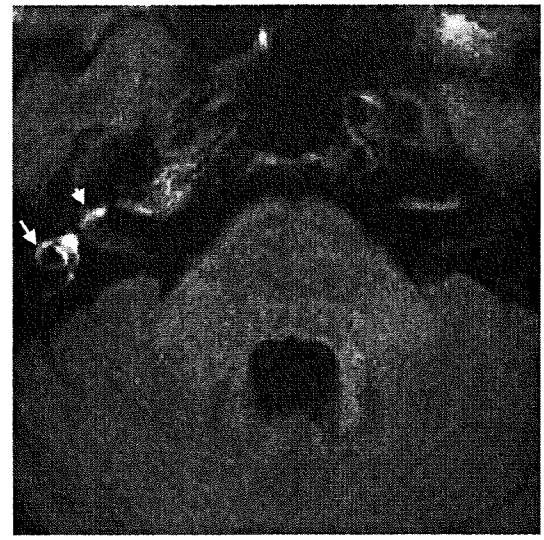

図1　ガドリニウム造影剤を8倍に薄めて右鼓室内に投与し，1日後に撮ったMRI所見(3D-FLAIR)
長い矢印は，外側半規管，短い矢印は蝸牛を示している．右側内耳の外リンパ腔全体に投与したガドリニウムが入っている．

8. 内耳局所療法の将来

内耳局所療法は，内耳血流量の観点からも，もっと検討されなければならない．マイクロウイックといって小さなろうそくの芯のようなものを鼓膜に開けた穴経由に蝸牛窓近くまで挿入し，その芯に薬をしみこませて内耳に薬剤を連続的に投与する方法も一部で行われている．また，特殊な薬剤をしみこませたゲルを内視鏡下に蝸牛窓の近くに置く方法も臨床試験されている．まだ，動物実験の段階であるが，感音難聴に対する遺伝子治療も，内耳への局所療法をどのように行っていくかという問題でもある．内耳手術で，現在もっとも普及しているのは人工内耳手術であるが，将来的には，より広い観点での内耳局所治療法の開発が求められている．

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ORIGINAL ARTICLE

Endolymphatic hydrops revealed by intravenous gadolinium injection in patients with Ménière's disease

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Abstract

Conclusion: Visualization of endolymphatic hydrops became possible after intravenous gadolinium (Gd) injection in patients with Ménière's disease. *Objective:* To visualize endolymphatic hydrops after intravenous Gd injection. *Methods:* Gd (gadoteridol; 0.2 mmol/kg) was injected intravenously in three patients with unilateral Ménière's disease. We performed three-dimensional fluid attenuated inversion recovery (3D-FLAIR) and three-dimensional real inversion recovery (3D-real IR) magnetic resonance imaging (MRI) 4 h after the injection using a 3-Tesla MRI unit. We used a 32-channel array coil to obtain a high signal-to-noise ratio. *Results:* Endolymphatic hydrops was observed in the ears of patients with Ménière's disease. However, Gd concentration in the perilymph was lower compared with that obtained after intratympanic Gd injection.

Keywords: *FLAIR, MRI, real IR MRI, intravenous gadolinium administration*

Introduction

Endolymphatic hydrops has been visualized after intratympanic gadolinium (Gd) injection using 3-Tesla magnetic resonance imaging (MRI) [1]. Gd enters the perilymphatic space through the round window membrane and can then delineate the perilymphatic and endolymphatic spaces. Three-dimensional fluid attenuated inversion recovery (3D-FLAIR) MRI and three-dimensional real inversion recovery (3D-real IR) MRI allow visualization of the endolymphatic space [2,3]. 3D-real IR MRI is generally better for visualizing the endolymphatic space than 3D-FLAIR MRI. However, when Gd concentration is not sufficient in the perilymph, it is more difficult to visualize the Gd in 3D-real IR MRI than in 3D-FLAIR MRI [4].

Gd is generally administered intravenously for contrast enhancement of MRI. If endolymphatic imaging by intravenous Gd injection becomes readily available, the intravenous method will be used widely [5]. At present, however, the signal-to-noise ratio is still insufficient to clearly demonstrate the endolymphatic space after ordinary intravenous Gd injection [6]. Gd concentration in the perilymph reaches its maximum level 4 h after intravenous administration of the drug [7]. Carfrae et al. [8] performed 3 T MRI 4 h after intravenous injection of a triple dose of Gd in normal subjects and patients with Ménière's disease. However, the resultant images were not convincing [9]. These authors did not perform 3D-FLAIR MRI. In this study, we attempted to visualize the endolymphatic space using 3D-FLAIR and 3D-real IR MRI carried out 4 h after intravenous injection of a double dose of Gd in patients with Ménière's disease.

Material and methods

Patients

Three patients with Ménière's disease were enrolled in this study (Table I). Case 1 was a 60-year-old woman who had had left fluctuating hearing loss

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Table I. Patients' details.

Case no.	Gender	Age (years)	Side	Average hearing level (dB)	Hearing fluctuation	Vertigo attacks	AAO-HNS classification
1	F	60	Right	115	No	Non-rotatory	Possible
			Left	68	Yes		
2	M	41	Right	20	Yes	Rotatory	Definite
			Left	6	No		
3	F	67	Right	62	Yes	Rotatory	Definite
			Left	13	No		

Average hearing level is average (dB) of three frequencies (500, 1000, and 2000 Hz). F, female; M, male.

and dizziness for 10 months. Because she had not experienced definitive episodes of rotatory vertigo, she was diagnosed as having possible Ménière's disease according to the criteria of the 1995 American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) [10]. Although she had left otitis media with a large perforation of the tympanic membrane, otorrhea was not recognized. When she was 58 years old, she underwent surgery to remove the right acoustic tumor via the posterior fossa, which was performed by a neurosurgeon. After the surgery, she lost right hearing ability completely. Her left average hearing level of three frequencies (500, 1000, and 2000 Hz) was 68 dB with an air–bone gap of 28 dB at the time she was examined by MRI.

Case 2 was a 41-year-old man with right fluctuating hearing loss. When he was 36 years old, he had low-tone sensorineural hearing loss on the right side without vertigo. Subsequently, he experienced fluctuation of his right hearing level. He had also had vertigo attacks, starting at 39 years of age. He had had three definite episodes of vertigo attacks and many drop attacks. He was diagnosed as having definite Ménière's disease according to the criteria of AAO-HNS. His right average hearing level of three frequencies was 20 dB with low-tone sensorineural hearing loss. The left hearing level was normal.

Case 3 was a 67-year-old woman. She had had four definite episodes of vertigo attacks with fluctuation of her right hearing level for 10 months. She was diagnosed as having definite Ménière's disease according to the criteria of AAO-HNS. Her right average hearing level of three frequencies was 62 dB with flat-type sensorineural hearing loss. The left hearing level was normal.

All patients gave informed consent to participate in this study. Their written informed consent was attached to the electronic medical record. The protocol of this study was approved by the Ethics Review Committee of the Nagoya University School of Medicine (approval number 587-2).

Intravenous Gd injection

Gadoteridol (ProHance®) was injected intravenously. The injected amount was 0.4 ml/kg (0.2 mmol/kg). Although the standard amount of gadoteridol is 0.2 ml/kg, a concentration of 0.4 ml/kg is permitted by the Japanese governmental health insurance system if the aim is to visualize metastatic brain tumors. At 4 h after the intravenous gadoteridol injection, MRI was performed.

MRI

MRI scans were performed with a 3 T MRI unit using a multichannel coil. We started with an 8-channel head coil and then switched to a 12-channel coil; we now use a 32-channel array coil to obtain a high signal-to-noise ratio [6]. Heavily T2-weighted 3D constructive interference in the steady-state imaging was obtained for anatomic reference and 3D-FLAIR was then performed to detect perilymph enhancement, while suppressing the signal from the endolymph. Finally, we obtained 3D-real IR images to visualize the endolymph, perilymph, and bone separately on a single image. The details of the MRI protocol were described previously [1–3]. In this study, the inversion time of the 3D-real IR images was extended up to 2000 ms, to adjust for the lower Gd concentration in the perilymph when compared with that delivered by intratympanic injection.

Results

In case 1, evaluation of endolymphatic space was possible in 3D-FLAIR and 3D-real IR MRI because Gd enhancement of the perilymph was relatively good on both sides. Significant endolymphatic hydrops was observed both in the cochlea and in the vestibule of the left ear (Figure 1). In the right ear, in which the acoustic tumor remained in the internal auditory canal (Figure 2), endolymphatic hydrops was not observed.

In case 2 the Gd enhancement was not as prominent as that observed in case 1. Evaluation of endolymphatic

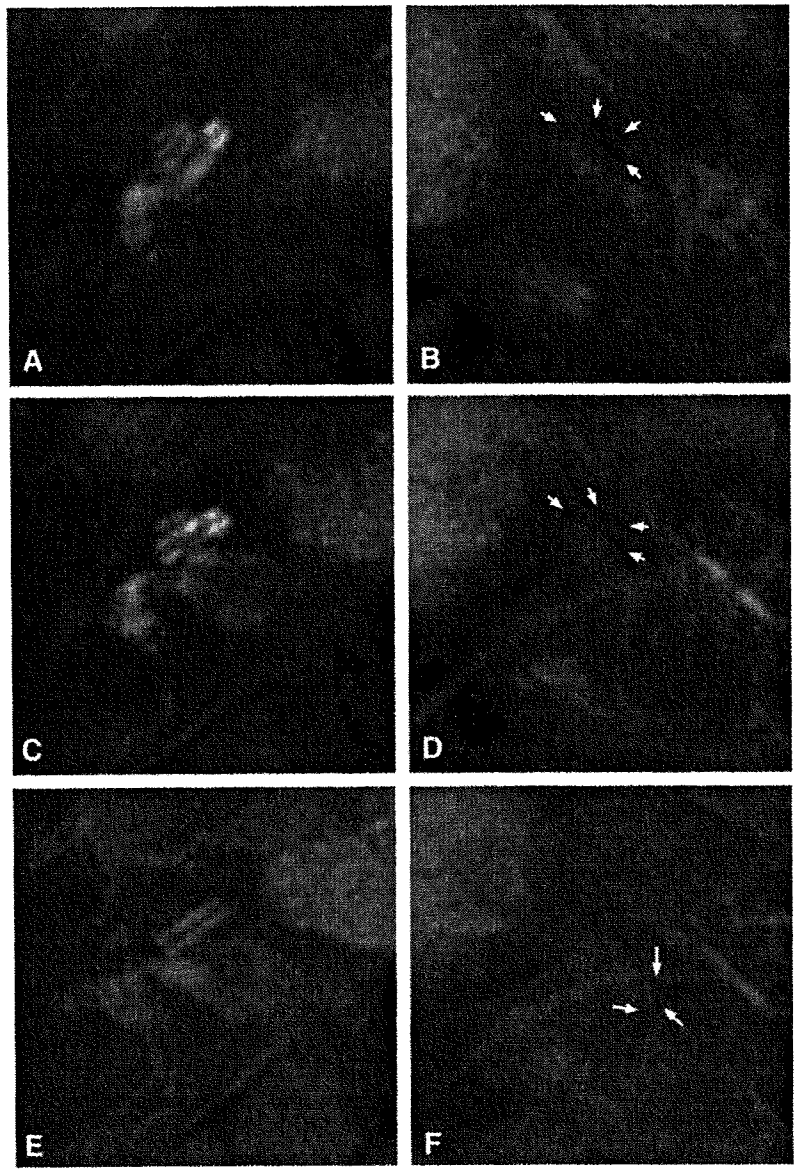

Figure 1. Consecutive sections of 3D-real IR MRI in case 1. A and B, C and D, and E and F are the same sections. A, C, and E show the right ear; B, D, and F show the left ear. Significant endolymphatic hydrops was observed in the left ear. Arrows in B and D indicate endolymphatic hydrops in the cochlea (black areas without Gd). Arrows in F indicate endolymphatic hydrops in the vestibule.

size was difficult in 3D-real IR MRI. However, significant hydrops was observed both in the cochlea and in the vestibule of the right ear in 3D-FLAIR MRI (Figure 3). Gd enhancement was much less evident in the normal left ear than in the right ear. No hydrops was recognized in the left ear.

In case 3, the Gd enhancement was clearer than that in case 2, but weaker than that in case 1. The Gd enhancement was barely recognized in 3D-real IR MRI. However, 3D-real IR MRI helped evaluation of the endolymphatic space size. Significant hydrops was observed both in the cochlea and in the vestibule of the right ear in 3D-FLAIR (Figure 4) and 3D-real IR MRI (Figure 5). Gd enhancement was less evident in the normal left ear than in the right ear. No hydrops was recognized in the left ear.

In all patients, endolymphatic hydrops was observed in the ear with fluctuating hearing loss. Both 3D-FLAIR MRI and 3D-real IR MRI were useful for evaluation of the size of the endolymphatic space.

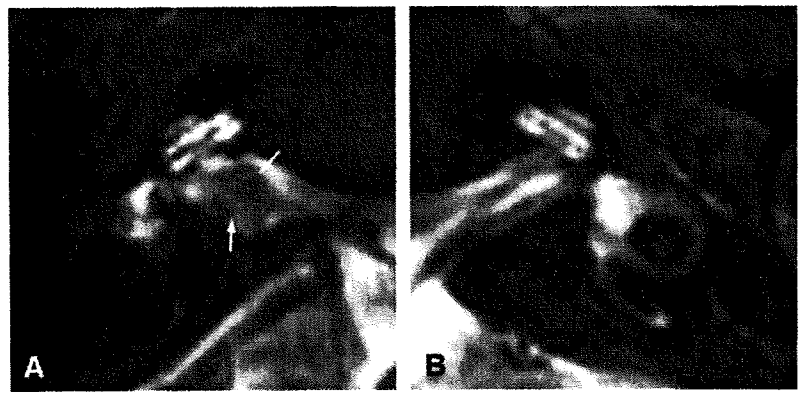

Figure 2. Heavily T2-weighted 3D constructive interference in the steady-state imaging of case 1. A, right ear; B, left ear. In these heavily T2-weighted images, both the endolymph and the perilymph are white and no differences were detected between the right and left ears. The remaining acoustic tumor of the right ear is indicated by arrows.

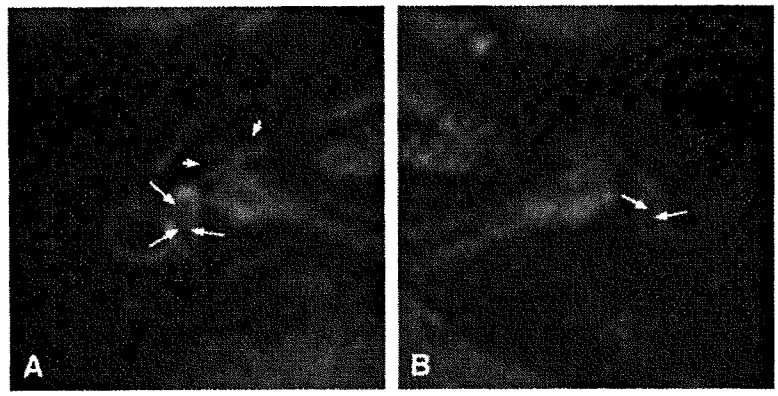

Figure 3. 3D-FLAIR MRI of case 2. A, right ear; B, left ear. In A, short arrows indicate endolymphatic hydrops in the basal turn of the cochlea (wedge-like areas). In 3D-FLAIR MRI, endolymphatic hydrops cannot be discriminated from the surrounding bone. In B, no cochlear hydrops is observed. In A and B, long arrows indicate endolymphatic space in the vestibule. The endolymphatic space is clearly larger in A than in B.

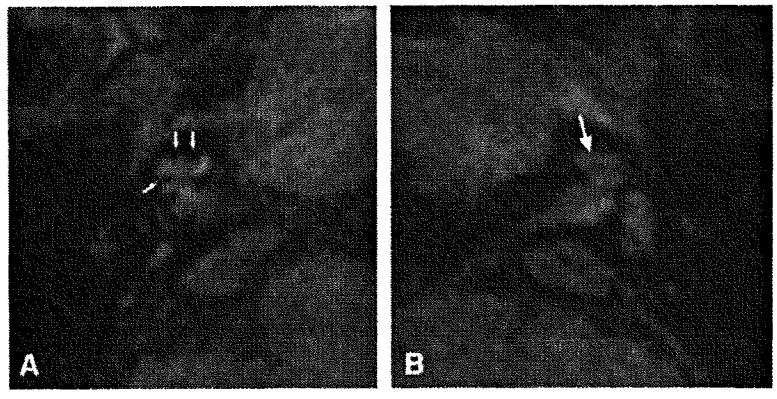

Figure 4. 3D-FLAIR MRI of case 3. A, right ear; B, left ear. In A, short arrows indicate endolymphatic hydrops in th basal and upper turns of the cochlea (wedge-like areas). In B, the cochlea shown by an arrow has no hydrops.

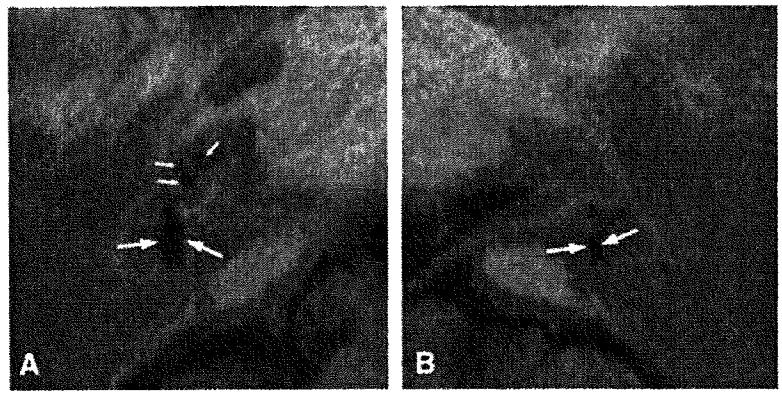

Figure 5. 3D-real IR MRI of case 3. A, right ear; B, left ear. In A, short arrows indicate endolymphatic hydrops in the basal and upper turns of the cochlea (black areas). In A and B, long arrows indicate endolymphatic space in the vestibule. The endolymphatic space is clearly larger in A than in B.

Discussion

We have successfully visualized endolymphatic hydrops after intravenous Gd injection. The blood-labyrinthine barrier includes the blood–endolymph barrier and blood–perilymph barrier. Because the blood–endolymph barrier is extremely tight compared with the blood–perilymph barrier, Gd administered intravenously enters the perilymph but does not enter the endolymph [11]. This difference made it possible to visualize the endolymphatic space of the inner ear in 3D-FLAIR and 3D-real IR MRI after intravenous injection of a double dose of Gd.

The Gd concentration in the perilymph was fainter than that observed after intratympanic injection of Gd diluted 8-fold, and seemed to be closer to the concentration observed after intratympanic injection of Gd diluted 16-fold. We were able to evaluate the degree of endolymphatic hydrops after intratympanic injection of the 16-fold dilution; however, to enhance image contrast, we are now using Gd diluted eightfold as the intratympanic injection method [4].

3D-real IR MRI was generally better than 3D-FLAIR MRI for visualizing the endolymphatic space, as the former discriminated the endolymphatic space not only from the perilymphatic space but also from the surrounding bone [2]. However, low Gd concentrations in the perilymph were more difficult to visualize by 3D-real IR MRI than by 3D-FLAIR MRI [4]. Accordingly, both 3D-FLAIR and 3D-real IR MRI are required for the precise evaluation of the endolymphatic space after intravenous Gd injection.

In case 1, intratympanic Gd injection was not suitable in the left ear because of a large perforation of the tympanic membrane. Intravenous Gd administration was necessary for the image diagnosis of endolymphatic hydrops. The Gd enhancement in the right ear with acoustic tumor was clear. This was probably due to the disrupted blood–labyrinthine barrier in the ear with acoustic tumor. In cases 2 and 3, the Gd enhancement was higher in the ear with Ménière's disease than in the normal ear. We can now evaluate the blood–labyrinthine barrier by intravenous injection of Gd.

Conclusion

We successfully visualized endolymphatic hydrops using 3D-FLAIR and 3D-real IR MRI performed 4 h after intravenous injection of a double dose of Gd, although the quality of the image was not as good as that obtained after intratympanic injection of Gd diluted eightfold with saline. The intravenous administration method, which has high applicability in clinical use, will be used to evaluate the endolymphatic space and the blood–labyrinth barrier on both sides.

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Changes in endolymphatic hydrops in a patient with Meniere's disease observed using magnetic resonance imaging

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Abstract

We describe a case report of a patient with Meniere's disease whose changes in endolymphatic hydrops were observed using magnetic resonance imaging (MRI). Gadolinium was injected intratympanically through the tympanic membrane, and MRI scans performed with a 3-T MRI unit revealed endolymphatic hydrops inside the perilymphatic space filled with gadolinium. We evaluated the relationship between the image findings and hearing level. The correlation between the degree of endolymphatic hydrops observed by MRI and hearing level in patients with Meniere's disease offers a promising new method to study the progression of Meniere's disease.

Keywords: Meniere's disease; Endolymphatic hydrops; Magnetic resonance imaging; Gadolinium; Hearing level

1. Introduction

Endolymphatic hydrops are recognized as the main pathological change of Meniere's disease. Many animal studies and human temporal studies have focused on changes in inner ear function associated with endolymphatic hydrops. Clinically, the severity of endolymphatic hydrops in a patient with Meniere's disease should be estimated in relation to the hearing level, and the results of electrocochleography (EcochG) or vestibular-evoked myogenic potential (VEMP) because pathological examination of the inner ear is not possible.

One report detailed the imaging analysis of the inner ear in patients with Meniere's disease using magnetic resonance imaging (MRI) with intratympanic administration of gadolinium [1]. The clinical imaging of endolymphatic hydrops using 3-T three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) MRI was recently reported [2]. A correlation between the degree of endolymphatic hydrops observed by MRI and clinical symptoms in patients with Meniere's disease offers a promising new method to study the progression of Meniere's disease.

We describe a case report of a patient with Meniere's disease whose changes in endolymphatic hydrops were observed using MRI. We evaluated the relationship between image findings and hearing level.

2. Case report

A 41-year-old man was referred to our department because of Meniere's disease in his left ear, which had begun two years earlier. He had sensorineural hearing loss of 30 dB on the left side. Since the first visit, his hearing level deteriorated gradually so that he experienced rotatory vertigo attacks despite medical treatment, which forced him to close his business for 1 year. During this down period, he received intratympanic gentamicin injection six times in total, and he was able to return to work without experiencing severe vertigo attacks. A caloric test with ice water after gentamicin injection showed no response on the left side.

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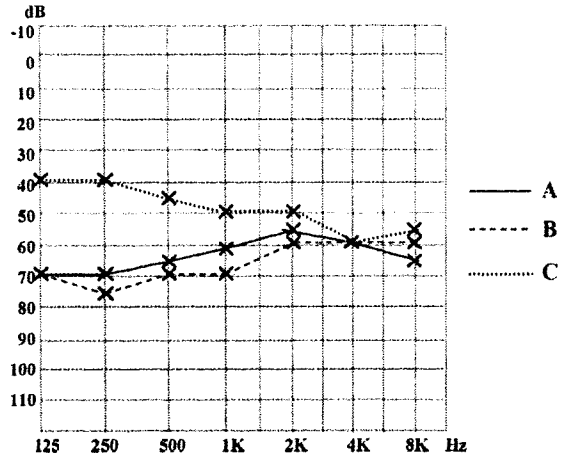

Fig. 1. Hearing levels on pure tone audiometry at the time of the initial (A), second (B), and third (C) magnetic resonance image examinations.

Two years after the treatment, the patient complained of frequent drop attacks. His hearing level at that time was 55–70 dB (Fig. 1A). A VEMP test and EcochG were performed at this time. 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). EcochG was performed with a silver ball electrode placed on the posteroinferior quadrant of the external ear canal, close to the tympanic membrane. The click stimuli were presented four times a second with rarefaction and condensation polarity (Synax 2100). The signal was added 500 times through the bandpass filter (100–3000 Hz). VEMP was absent, and the SP/AP ratio on EcochG was 48%.

To investigate the patient's inner ear condition more completely, gadodiamide hydrate (Omniscan®, Daiich Pharmaceutical Co. Ltd, Tokyo, Japan) diluted eightfold with saline was injected intratympanically through the tympanic membrane, and MRI scans were performed with a 3-T MRI unit (Trio, Siemens, Erlangen, Germany) 24 h after the injection [2]. The patient gave written informed consent to participate in this MRI examination in accordance with the suggestion of the Ethics Review Committee.

3D-FLAIR MRI revealed significant endolymphatic hydrops inside the perilymphatic space filled with gadolinium, which was observed in the lower and upper turns of the cochlea (Fig. 2A) [3]. The gadolinium was faintly visible in the vestibule and the lateral semicircular canal. Seven months after the first gadolinium injection, his hearing level recovered to 45 dB without drop attacks, and a second MRI examination with gadolinium injection was planned. However, a few weeks before the second examination, his hearing level began to deteriorate to 60–75 dB, especially at lower frequencies

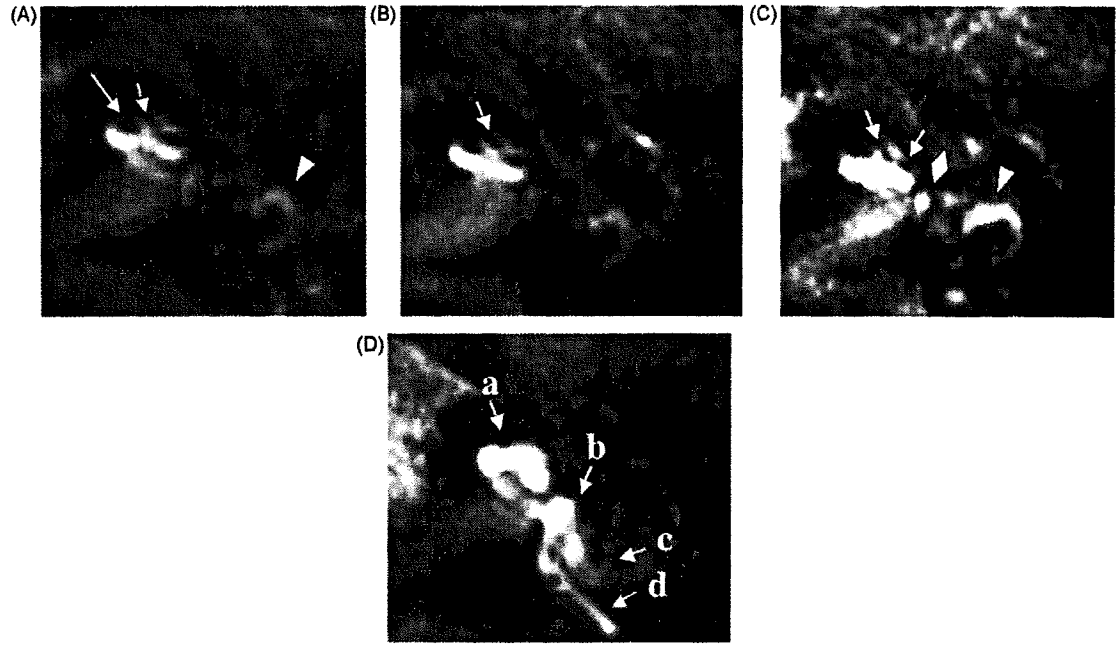

Fig. 2. Three-dimensional fluid-attenuated inversion recovery magnetic resonance images on the axial plane. (A) The initial image shows endolymphatic space inside the perilymphatic space filled with the gadolinium in the lower (long arrow) and upper (short arrow) turns of the cochlea, and faintly visible gadolinium in the lateral semicircular canal (arrowhead). (B) The image at the second examination shows endolymphatic hydrops to a similar degree as that observed in the first MRI, and the hydrops in the upper turn of the cochlea is obvious (short arrow). (C) The image at the third examination shows reduced endolymphatic space in the cochlea (short arrows) and more strongly visible gadolinium in the vestibule (diamond) and the semicircular canal (arrowhead). (D) An image from a patient with acute sensorineural hearing loss with no endolymphatic hydrops is given as an example for comparison. (a) The cochlea, (b) the vestibule, and (c) the lateral and (d) posterior semicircular canals. The endolymphatic space is not clearly visible in this case.

(Fig. 1B), and he experienced drop attacks once more. 3D-FLAIR MRI revealed endolymphatic hydrops to a similar degree as that observed in the first MRI (Fig. 2B). He was treated with medication including a diuretic, and his hearing level improved and stabilized at 40–50 dB, especially at lower frequencies, and he experienced no further drop attacks (Fig. 1C). A third 3D-FLAIR MRI examination was performed 15 months after the second examination and it revealed reduced endolymphatic hydrops in the cochlea (mild hydrops) compared with that observed in the two previous examinations (significant hydrops) [3]. The gadolinium was more strongly visible in the vestibule and the semicircular canals (Fig. 2C). The hearing level on the right side was within the normal range throughout this period. Vestibular findings, such as nystagmus, were not observed in the patient during the follow-up periods using MRI, except for the patient's experience of drop attacks. The VEMP test and EcochG were not performed during the second and third MRI examinations.

3. Discussion

MRI with intratympanic administration of gadolinium can be used for imaging analysis of the inner ear in patients with Meniere's disease [1]. The clinical imaging of endolymphatic hydrops using 3-T 3D-FLAIR MRI was also reported [2]. Intratympanically administered gadolinium moves into the scala tympani of the basal turn of the cochlea and the perilymphatic space of the vestibule, and the border between the perilymph and endolymph is clearly visible in 3D-FLAIR MRI taken 24 h after the injection [2]. 3D-FLAIR MRI is sensitive enough to detect inner ear disturbances [4,5].

Our patient's hearing level, especially at lower frequencies, had fluctuated along with equilibrium disturbance, which are typical symptoms of Meniere's disease. 3D-FLAIR MRI showed the changing severity of the endolymphatic hydrops and that this correlated with changes in the patient's hearing level. That is, the observed enlarged or reduced endolymphatic hydrops, especially in the upper turns, correlated with deterioration or improvement of his hearing thresholds at lower frequencies. Importantly, the gadolinium was more clearly visible in the vestibule on the third MRI, suggesting that the reduced endolymphatic hydrops in the vestibule enabled the movement of the gadolinium from the scala tympani of the cochlea to the vestibule. Pathophysiologically, a drop attack might occur when the endolymphatic hydrops involves the vestibule.

Pathological changes of Meniere's disease include endolymphatic hydrops and abnormalities in the cochlear lateral wall, hair cells, and spiral ganglion. Endolymphatic hydrops may be considered a histological marker for Meniere's disease rather than being directly responsible for its symptoms [6]. Endolymphatic hydrops observed with MRI could provide useful information for the treatment of patients diagnosed with Meniere's disease. No adverse effects of the intratympanic injection of gadolinium have been observed so far, and this procedure is considered a safe method with no ototoxicity [7].

We are planning further investigations to evaluate more precisely the relationship between images of the endolymphatic space and clinical findings on a large number of patients with Meniere's disease. We will collect data on the changes of hearing level, direction of nystagmus, VEMP, and EcochG.

Acknowledgements

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OTOLOGY

Image evaluation of endolymphatic space in fluctuating hearing loss without vertigo

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Abstract The objective of the present study was to investigate endolymphatic space images in patients with fluctuating hearing loss without vertigo, and to elucidate its underlying pathophysiology. Eight patients with fluctuating hearing loss without vertigo were included in this study. 3T MRI was taken, 24 h after intratympanic injection of gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA). Electrocochleography and VEMP tests were performed to evaluate cochlear and vestibular functions. Endolymphatic hydrops were observed both in the cochlea and in the vestibule of all eight patients. Three patients out of six whose summating potential/action potential (SP/AP) ratio was recordable showed an elevation of SP/AP ratio. In the two patients with remarkable endolymphatic hydrops in the vestibule, VEMP was absent from the affected ear. In conclusion, 3T MRI after intratympanic injection of Gd-DTPA revealed endolymphatic hydrops both in the cochlea and in the vestibule in the patients with fluctuating hearing loss without vertigo.

Keywords Fluctuating hearing loss without vertigo · MRI · Endolymphatic space · Electrocochleography · VEMP · Meniere

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Introduction

Fluctuating hearing loss without vertigo is frequently termed as cochlear Meniere's disease. Meniere's disease is a syndrome characterized by repeated vertiginous spells accompanied by fluctuating hearing loss and aural fullness. Hallpike and Yamakawa almost simultaneously, but independently, reported an enlarged endolymphatic space in the temporal bones of patients with Meniere's disease, demonstrating that endolymphatic hydrops are its principal underlying pathology [1, 2]. As well as classic or typical Meniere's disease, which shows repeated vertigo, hearing loss and aural fullness, atypical Meniere's disease exists, which shows fluctuating hearing loss without vertigo or repeated vertigo without hearing loss. Atypical Meniere's disease involving fluctuating hearing loss without vertigo was defined as cochlear Meniere's disease by the subcommittee on equilibrium and its measurement of the American Academy of Ophthalmology and Otolaryngology (AAOO) in 1972 [3]. Williams reported patients that show solely cochlear symptoms as endolymphatic hydrops without vertigo [4]. Some previous case reports that investigated the temporal bones of patients showed endolymphatic hydrops, suggesting that it is involved in the pathology of both cochlear Meniere's disease and classic Meniere's disease [5–7]. However, in 1985, the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) decided to limit the diagnostic term "Meniere's disease" to those patients with the full complement of classic symptoms and exclude the variants of Meniere's disease that are referred to as cochlear and vestibular Meniere's disease. This exclusion was based on an absence of documentation that these variants are based on the same pathological disorder as Meniere's disease [8]. Thus, the exact definition of variants of

Meniere's disease continues to be controversial. According to the most recent definition by AAO-HNS in 1995, cochlear variants with disequilibrium are classified as possible Meniere's disease. In the AAO-HNS criteria in 1995, certain Meniere's disease requires histological pathological confirmation after autopsy [9]; objective diagnosis with histological confirmation is now virtually impossible for live patients. Recently, we established an endolymphatic space imaging using 3T MRI after intratympanic injection of gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA). Gd-DTPA distributes widely in the perilymphatic space of both cochlea and vestibule 24 h after intratympanic injection. The enlarged endolymphatic space without Gd-DTPA distribution has been recognized as an area of low-signal intensity surrounded by high-signal perilymphatic fluid with Gd-DTPA distribution in patients with Meniere's disease [10–13]. Therefore, MRI after intratympanic injection of Gd-DTPA is a promising alternative for the histological confirmation of endolymphatic hydrops. We have undertaken the present study to investigate endolymphatic space images in patients with fluctuating hearing loss without vertigo, and to elucidate its underlying pathophysiology.

Materials and methods

Patients

Eight patients, who showed fluctuation of unilateral hearing loss without vertiginous spells and met the 1972 AAOO criteria for cochlear Meniere's disease [3], were enrolled in this study. Age, sex, affected side, and average hearing level at 500 Hz, 1, and 2 kHz are presented in Table 1. Each patient underwent intratympanic administration of gadolinium-diethylenetriamine pentaacetic acid bis(methylamide) (Gd-DPTA-BMA; Omniscan, Daiichi Pharmaceutical Co., Tokyo, Japan) in the affected ear. The protocol of the study was approved by the Ethics Review Committee of Nagoya University School of Medicine. All patients gave their informed consent to participate in this study. Each patient's written informed consent was attached to his or her electronic medical record after permission was given.

Intratympanic gadolinium injection

The detailed methods for intratympanic gadolinium injection have been reported previously [10]. Gd-DPTA BMA was diluted eightfold with saline (v/v 1:7). The diluted Gd-DPTA BMA was injected through the tympanic membrane using a 23-G needle and a 1-ml syringe after the patient was placed in the supine position with the head turned approximately 30° away from the sagittal line toward the other ear. The injection was performed under a microscope. The amount of diluted gadolinium injected was 0.4–0.5 ml. After the injection, the patient remained in the supine position for 60 min with the head turned approximately 60° away from the sagittal line toward the other ear.

MR imaging

According to the results from the previous study, scan delay after intratympanic gadolinium injection was determined as 24 h to allow the distribution of gadolinium widely in the perilymphatic space of the labyrinth [10]. MRI scans were performed with a 3T MR unit (Trio, Siemens, Erlangen, Germany) using a receive-only 12-channel phased-array coil. As described previously [11–13], T1-weighted 3D-FLASH (fast low-angle shot) and conventional 3D-FLAIR (fluid-attenuated inversion recovery) imaging was performed. T2-weighted 3D-CISS (construc-

Table 1 Summary of clinical and MRI findings

Case number	Age, gender	Affected side	Hearing levels (dB)	Vestibular symptoms	SP/AP (%)	VEMP	Size of endolymphatic space in cochlea	Size of endolymphatic space in vestibule
1	31, M	Right	25, 37	None	Not performed	Normal	2	1
2	60, F	Right	20, 37	None	43	Not performed	1	1
3	45, M	Right	52, 63	Dizziness	21	Noise level	2	1
4	65, M	Left	50, 55	None	Not recordable	Noise level	2	2
5	54, M	Left	23, 23	None	30	Normal	2	1
6	44, F	Right	38, 42	Dizziness	41	Noise level	2	1
7	69, F	Left	22, 23	None	55	Noise level	2	2
8	44, F	Left	13, 28	None	23	Normal	1	1

Hearing levels indicates average of hearing level of 500 Hz, 1, 2 kHz and average of hearing level of 250, 500 Hz, 1 kHz

Size of endolymphatic space in cochlea and in vestibule: *0* no endolymphatic hydrops, *1* mild endolymphayic hydrops, *2* significant endolymphatic hydrops

SP/AP summating potential/action potential on electrocochleography, *VEMP* vestibular evoked myogenic potential

tive interference in the steady state) imaging was performed to obtain reference images of labyrinthine fluid-space anatomy. 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° (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^2 field of view, acquired using the GRAPPA parallel imaging technique with an acceleration factor of 2 [14]. The number of excitations was one, and the scan time was 14 min. As previously described [12], TI of 1,000 ms was selected for 3D inversion-recovery imaging of the 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 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.

Image evaluation of endolymphatic space in MRI

The size of the endolymphatic space was scored according to the reports on the MRI by radiologists who did not know the corresponding clinical information. Scoring was performed using the following criteria. In the vestibule, a score of 2 indicates a remarkable enlargement of endolymphatic space that occupied more than half of the vestibule. A score of 1 indicates a moderate enlargement of endolymphatic space that occupied between 33.3 and 50% area of the vestibule. A score of 0 indicates no or very mild if any enlargement of endolymphatic space that occupied < 33.3% of the vestibule. In the cochlea, a score of 2 indicates a remarkable enlargement of endolymphatic space whose size is as large as or larger than the scala vestibuli. A score of 1 indicates a moderate enlargement of endolymphatic space. Reissner's membrane was bulging toward the scala vestibuli, although the endolymphatic space is smaller than the perilymphatic space of the scala vestibuli. A score of 0 indicates no or very mild if any enlargement of endolymphatic space. No bulging of Reissner's membrane was shown or no endolymphatic space was observed. These tentative criteria were established according to previous histological research in humans and animals [12, 13, 15–17].

EcochG (extratympanic electrocochleography)

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 (Biotech, 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 or her head toward the contralateral side in the sitting position to activate the sternomastoid muscle.

Results

Table 1 summarizes patients' clinical and imaging results. Eight patients (four male, four female) were included in this study. Their average age was 51.5 years, with a range of 31–69 years. All the patients experienced fluctuating hearing loss. Figure 1 shows audiograms of each case to demonstrate the best and the worst hearing levels on the affected ear during our observation, so that how far hearing threshold fluctuated in our patients can be recognized. Six patients experienced no vestibular symptoms (no vertigo or dizziness). Two patients experienced subtle dizziness, but no Meniere-type vertigo spells. Endolymphatic hydrops were observed both in the cochlea and in the vestibule of all the eight patients with cochlear Meniere's disease. The evaluation for cochlear alteration/enlargement of endolymphatic space was determined in basal, middle, and apical turns of the cochlea, if the gadolinium was distributed in the perilymph of all cochlear turns and endolymphatic space was recognized. In all the cases except case 2, the extent of endolymphatic hydrops does not differ among each cochlear turn. In case 2, gadolinium was distributed only in the basal turn and endolymphatic space was determined only in the basal turn. Three patients (cases 2, 6, and 7) out of six whose SP/AP ratio was recordable showed an

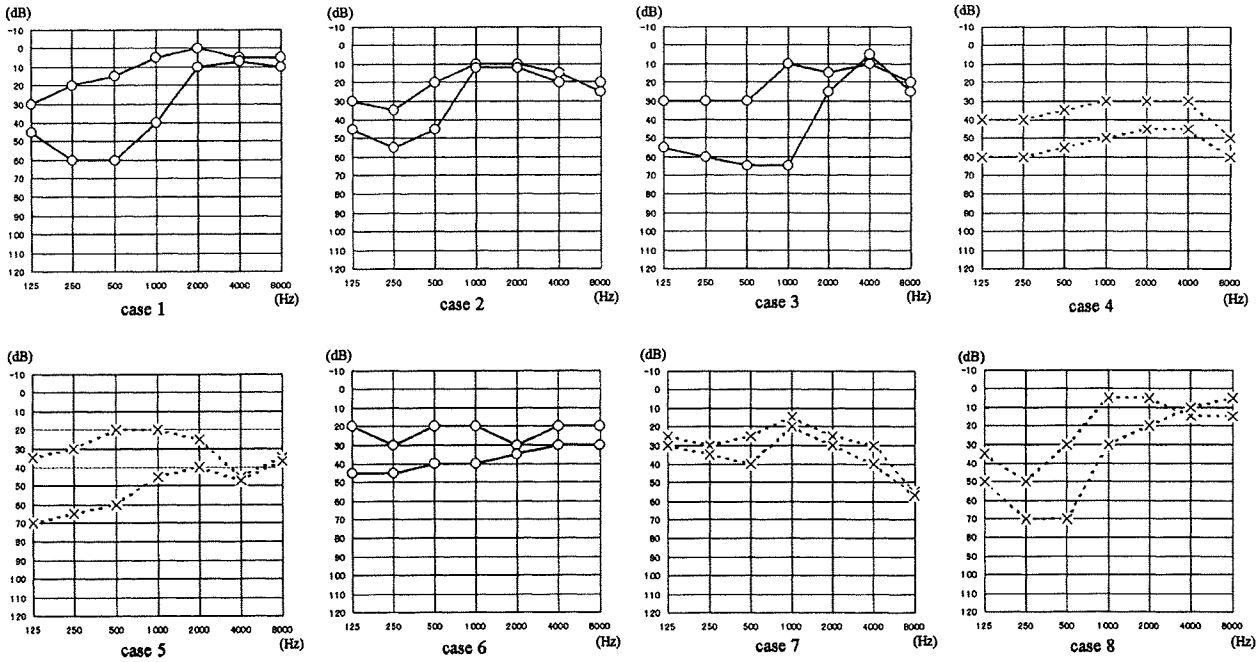

Fig. 1 Audiograms on the affected ear of the eight cases. The best hearing level and the worst one during our observation were shown. The vertical axis indicates hearing level (dB) on air conduction and the horizontal axis indicates each frequency (Hz). *o* right side of the ear, *x* left side of the ear

elevation of SP/AP ratio. In the two patients (cases 4 and 7) with remarkable endolymphatic hydrops in the vestibule, VEMP was absent from the affected ear. Among the five patients with moderate endolymphatic hydrops who underwent the VEMP test, the response was absent in two patients (cases 3 and 6) and the response was present in three patients (cases 1, 5, and 8) in the affected ears. No side effects related to the intratympanic injection of Gd-DTPA such as worsening of hearing level or tinnitus was observed.

Figure 2 shows MR images of a 45-year-old man (case 3). He experienced repeated aural fullness and fluctuation of hearing loss at low frequencies. He also felt slight dizziness from time to time. SP/AP ratio from electrocochleography was 21% and VEMP response was absent from the affected side. 3D-FLAIR shows an enlarged endolymphatic space in the cochlea as low signal areas. However, the boundary between the endolymphatic space and surrounding bone is unclear. Moderate enlargement of the endolymphatic space in the vestibule was observed. A 3D-real IR sequence visualizes remarkably enlarged endolymphatic space in the cochlea and moderately enlarged endolymphatic space in the vestibule as negative signal intensity values, while the surrounding bone area has near-zero signal intensity. This image allows the separation of the perilymphatic space (high signal intensity), endolymphatic space, and surrounding bone on a single plain, so that endolymphatic hydrops in all cochlear turns were identified.

Figure 3 shows MR images of a 54-year-old man (case 5). He experienced repeated aural fullness and fluctuation of hearing loss at low frequencies. He did not experience vestibular symptoms. The SP/AP ratio from electrocochleography was 30% and VEMP showed a normal response on the affected side. Remarkable endolymphatic hydrops are observed in the cochlea and moderate endolymphatic hydrops are observed in the vestibule.

Discussion

This study is the first report of image evaluation of endolymphatic space in fluctuating hearing loss without vertigo. We have shown in the present study that 3T MRI taken 24 h after intratympanic injection of Gd-DTPA revealed endolymphatic hydrops both in the cochlea and in the vestibule in all eight patients with cochlear Meniere's disease. Merchant et al. reported that seven out of eight patients with fluctuating or progressive sensorineural hearing loss in the absence of vertigo spells showed idiopathic endolymphatic hydrops both in the cochlea and in the vestibule of their temporal bones after autopsy, with one exception that showed endolymphatic hydrops only in the cochlea. They also demonstrated in the same study that all 26 patients with classic Meniere's symptom complex showed dilatation of the cochlear duct and the saccule, and the majority (65%) also had hydrops involving the utricle or the ampullae

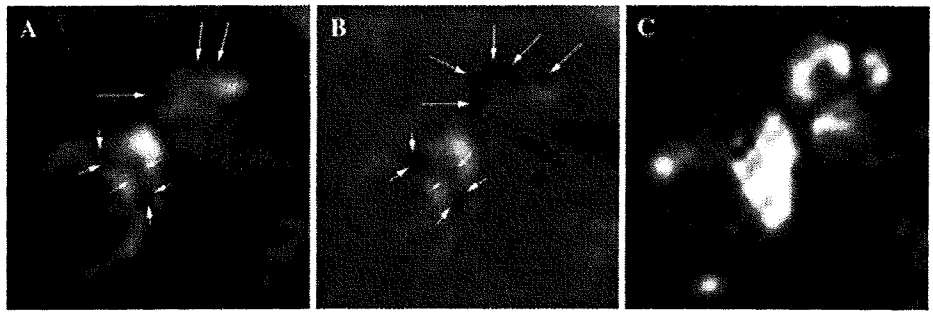

Fig. 2 MRI of case 3. **a** 3D FLAIR shows an enlarged endolymphatic space in the cochlea (*arrows*) as a low signal area. However, the boundary between the endolymphatic space and surrounding bone is unclear. Moderate enlargement of the endolymphatic space in the vestibule (*short arrows*) was observed. **b** A 3D-real IR sequence visualizes remarkably enlarged endolymphatic space in the cochlea (*arrows*) and moderately enlarged endolymphatic space in the vestibule (*short arrows*) as negative signal intensity values, while the surrounding bone area has near-zero signal intensity. Endolymphatic hydrops in all cochlear turns were identified. **c** 3D-CISS image shows the combination of endolymphatic and perilymphatic space

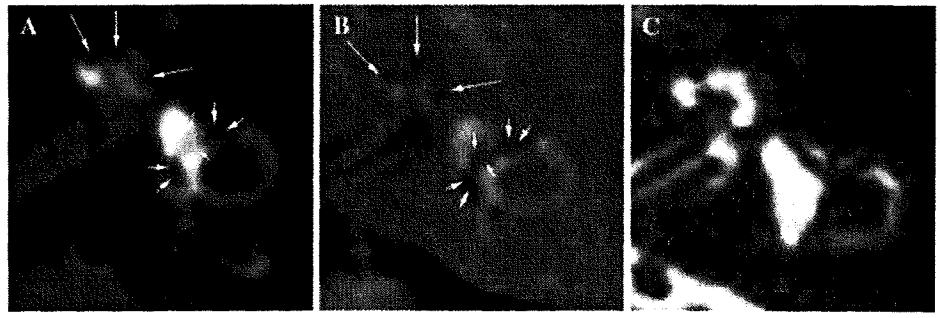

Fig. 3 MRI of case 5. **a** 3D FLAIR shows enlarged endolymphatic space in the cochlea (*arrows*) as low signal areas. However, the boundary between the endolymphatic space and surrounding bone is unclear. Moderate enlargement of the endolymphatic space in the vestibule (*short arrows*) was observed. **b** A 3D-real IR sequence visualizes remarkably enlarged endolymphatic space in the cochlea (*arrows*) and moderately enlarged endolymphatic space in the vestibule (*short arrows*) as negative signal intensity values, while the surrounding bone area has near-zero signal intensity. **c** 3D-CISS image shows the combination of endolymphatic and perilymphatic space

[18]. We recently reported that 3T MRI 24 h after intratympanic injection of Gd-DTPA revealed endolymphatic hydrops both in the cochlea and in the vestibule in all six patients with classic Meniere's disease [13]. The pathophysiological essence of Meniere's disease is endolymphatic hydrops. The existence of cochlear Meniere's disease has been questioned because of lack of evidence on its association with endolymphatic hydrops [8, 19]. Judging from our present study and a recent temporal bone study by others, cochlear Meniere's disease is truly a subtype of Meniere's disease and a similar pathophysiological mechanism is involved in both classic and cochlear Meniere's disease. The only difference is the manifestation of symptoms. Clinical and pathological evidence supports the existence of symptomatic and asymptomatic forms of endolymphatic hydrops. About one-third of the contralateral ears showed asymptomatic endolymphatic hydrops in patients with unilateral Meniere's disease by a temporal bone study after autopsy [20]. Schuknecht et al. reported that the endolymphatic hydrops must be progressive, thereby causing ruptures and distortion of the labyrinth, if they are symptomatic [21]. So far, we have no way of establishing whether the hydrops in asymptomatic cases are progressive or not. A 3T MRI after intratympanic injection of Gd-DTPA has the potential of in vivo imaging to permit a systematic assessment of the dynamic events over time in patients with endolymphatic hydrops. The utriculo-endolymphatic valve is located in the anteroinferior wall of the utricle at the orifice of the utricular duct and its probable role is to maintain the anatomical and humoral independence of the pars superior (utricle and canals) from the pars inferior (cochlear duct and saccule). The utriculo-endolymphatic valve might protect the vestibular apparatus from the hydropic condition [19, 22]. A substantial number of patients (80%) with cochlear Meniere's disease eventually proceed to classic Meniere's disease [23]. People under mental stress show an elevation of plasma level of stress-related hormone, vasopressin [24, 25]. Patients with endolymphatic hydrops-related diseases such as Meniere's disease also show an elevation of plasma level of vasopressin [26]. Guinea pig or rats treated systemically with vasopressin showed remarkable endolymphatic hydrops in the inner

ear compared with controls [27, 28]. Patients with cochlear Meniere's disease could have vertigo spells eventually, via progression of endolymphatic hydrops if they continue to be under stress.

We have performed functional tests, including EcochG, to assess cochlear function and a VEMP test to assess vestibular function [29, 30]. Elevation of the SP/AP ratio by more than 36% is considered positive for cochlear endolymphatic hydrops [13, 31]. In the present study, three patients (50%) out of six whose SP/AP ratio was recordable showed an elevation of SP/AP ratio. Dornhoffer previously reported that six of nine ears (67%) with cochlear Meniere's disease showed abnormal EcochG results suggestive of endolymphatic hydrops, which is similar to our present study [19]. Using click SP/AP ratio, the false negative results reach 54%, if the hearing level is less than 40 dB. Further utilization of tone burst data will make EcochG more sensitive. By using the norms established for 1,000 Hz, false negative results are reduced to 23% [32]. Introduction with other frequencies using tone burst will further increase the sensitivity of EcochG [19, 33]. A positive VEMP response is considered a normal sign of vestibular function, especially for the saccule. Lin reported the usefulness of the VEMP test to detect asymptomatic saccular hydrops [30]. However, we did not perform caloric tests to evaluate vestibular function transmitted by the pars superior of the vestibular nerve. This is the limitation of our study. Among the five patients with moderate endolymphatic hydrops who underwent a VEMP test, a VEMP response was absent in two patients (40%) in the affected ear. On the other hand, in the two patients with remarkable endolymphatic hydrops in the vestibule, a VEMP response was absent from the affected ears of both patients (100%). This may imply that the presence or absence of VEMP reflects the severity of vestibular endolymphatic hydrops. The existence of VEMP depends also on the degree of hearing loss, especially in lower frequencies as previously reported [34]. The two patients whose VEMP response was present among five patients with mild vestibular endolymphatic hydrops had better average hearing level of 250 Hz, 500 Hz, 1 kHz than the three patients whose VEMP was absent. Hearing level in lower frequencies might have influenced the presence or absence of VEMP in patients with mild vestibular endolymphatic hydrops.

In conclusion, 3T MRI after intratympanic injection of Gd-DTPA revealed endolymphatic hydrops both in the cochlea and in the vestibule in patients with cochlear Meniere's disease, a true variant of classic Meniere's disease.

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ORIGINAL ARTICLE

3D computerized model of endolymphatic hydrops from specimens of temporal bone

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Abstract

Conclusion: The 3D models of endolymphatic and perilymphatic spaces enabled us to obtain normal and pathological volumes of each space and helped us to understand the 3D structure of various parts of the inner ear and of endolymphatic hydrops. *Objective:* To make a 3D model of the inner ear using sections of temporal bone with and without hydrops. *Materials and methods:* Every 10th 20 μm thick section of temporal bone was collected from two ears with endolymphatic hydrops and five ears without hydrops. Using ZedView, 3D Doctor, FreeForm as analytical software, a 3D model of the inner ear was obtained by reconstruction of these sections. The volumes of the endolymphatic (EV) and perilymphatic spaces (PV) were calculated in each part of the cochlea and vestibular apparatus including the semicircular canals, but the endolymphatic duct and sac were not included. *Results:* In normal ears (controls), the average cochlear EV was 5.1 μl and the PV was 41.9 μl, and the average vestibular EV was 24.0 μl and the PV 75.7 μl. In one hydropic ear, the cochlear EV was 17.5 μl, cochlear PV 30.7 μl, vestibular EV 42.5 μl, and vestibular PV 33.4 μl. In the other hydropic ear, cochlear EV was 31.2 μl, cochlear PV 30.1 μl, vestibular EV 25.6 μl, and vestibular PV 71.8 μl.

Keywords: *Three-dimensional model, endolymphatic space, perilymphatic space, endolymphatic hydrops, temporal bone specimen*

Introduction

A 3D model of the human inner ear is an important tool to aid our understanding of normal physiologic processes as well as their modification during disease [1]. Therapy using intratympanic gentamicin is now widely used for the treatment of intractable Meniere's disease, and intratympanic therapy using steroids has been used to treat Meniere's disease or sudden deafness. A 3D model of hydrops in the inner ear will be helpful in understanding the underlying pathology of Meniere's disease and the pattern of distribution of locally applied drugs such as gentamicin and steroids. In this study we compared the volume of endolymph and perilymph in temporal bones with and without endolymphatic hydrops.

Materials and methods

We used two ears with endolymphatic hydrops and five ears without hydrops from the collection of temporal bones at the University of Minnesota. Clinical information about these patients is shown in Table I. Every 10th 20 μm thick section of temporal bone was studied (Figure 1), using ZedView, 3D Doctor, FreeForm as the analytical software. The 3D reconstruction of the inner ear was performed through segmentation of the endolymphatic and perilymphatic spaces (Figure 2). Endolymphatic volume (EV) and perilymphatic volume (PV) were calculated in each part of the cochlea and in the vestibular apparatus, including the semicircular canals. However, the endolymphatic duct and sac were not investigated because of

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Table I. Clinical information for the cases studied.

Case no.	Age, gender	Cause of death	Ear
1	77, female	Lung cancer, hepatoma	Endolymphatic hydrops, otosclerosis
2	78, female	Traffic accident	Endolymphatic hydrops, otosclerosis
3	72, male	Cancer, origin unknown	Control
4	74, male	Myocardial infarction	Control
5	67, female	Unknown	Control
6	59, female	Myocardial infarction	Control
7	59, female	Cancer of uterus	Control

difficulty of reconstruction from every 10th section in this area.

Results

In the five ears used as controls, average cochlear EV was 5.1 μl, and average cochlear PV was 41.9 μl.

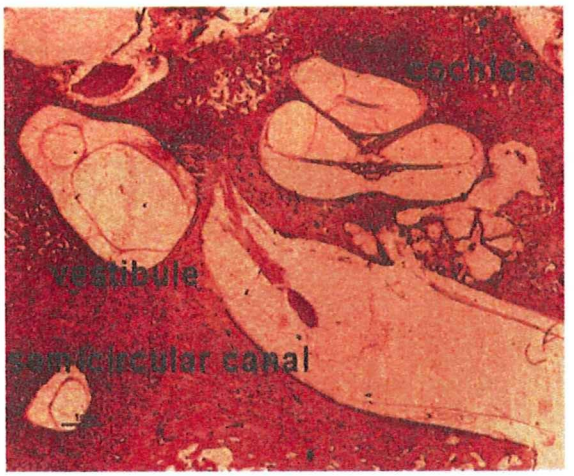

Figure 1. Section of an ear with endolymphatic hydrops.

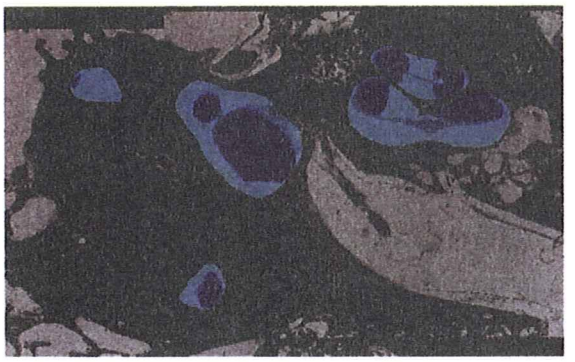

Figure 2. Segmentation of endolymphatic and perilymphatic spaces. Dark blue areas indicate endolymphatic spaces and light blue areas indicate perilymphatic spaces (case 1).

Table II. Endolymphatic and perilymphatic volumes in the inner ear.

Case no.	Cochlear EV (μl)	Cochlear PV (μl)	Vestibular EV (μl)	Vestibular PV (μl)
1 (hydrops)	17.5	30.7	42.5	33.4
2 (hydrops)	31.2	30.1	25.6	71.8
3 (control)	5.5	36.9	26.5	77.7
4 (control)	4.7	45.7	18.2	56.9
5 (control)	4.7	35.9	22.2	66.4
6 (control)	4.4	38.8	24.6	77.6
7 (control)	6.0	52.4	28.7	100.0

EV, endolymphatic volume; PV, perilymphatic volume.

Average vestibular EV in controls was 24.0 μl and average vestibular PV was 75.7 μl. The EV and PV in the inner ears of two hydropic and five control ears are shown in Table II and Figure 3. In one hydropic ear (case 1), the cochlear and vestibular EV was large compared with that in controls. In the other hydropic ear (case 2), the cochlear EV was large but vestibular EV was not large compared with that in controls.

3D models of endolymphatic hydrops (cases 1 and 2) and controls (cases 3 and 7) are presented in Figures 4–7. Figure 4 shows a 3D model of the inner ear of case 1 (with hydrops). This case demonstrates endolymphatic hydrops both in the cochlea and vestibule. Figure 5 shows a 3D model of the inner ear of case 2 (with hydrops). This case demonstrates endolymphatic hydrops only in the cochlea. Figures 6 and 7 show 3D models of the inner ears of cases 3 and 7 (controls). In these cases the endolymphatic space is not enlarged in either the cochlea or the vestibule.

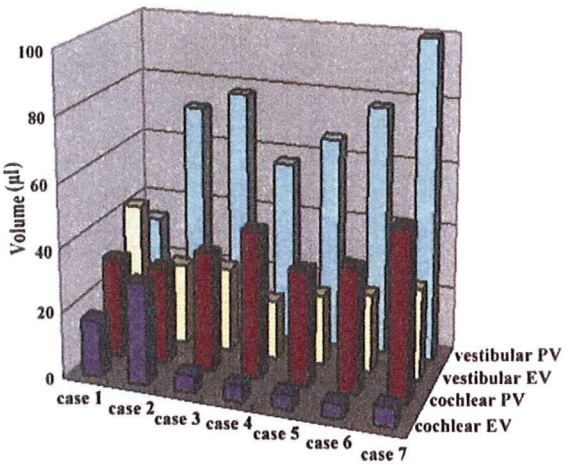

Figure 3. Graph demonstrating endolymphatic volume (EV) and perilymphatic volume (PV) in the inner ear. Case 1 indicates a higher EV than that in controls, both in the cochlea and in the vestibule. Case 2 indicates a higher EV than in controls in the cochlea, but not in the vestibule. Controls: cases 3, 4, 5, 6, and 7.

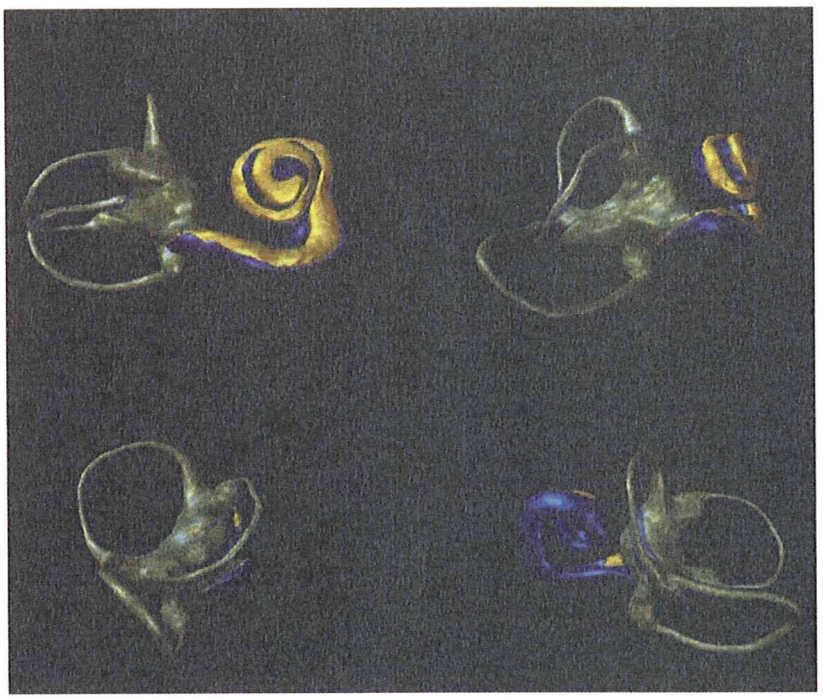

Figure 4. A 3D model of the inner ear of case 1 (with hydrops). Blue area indicates perilymphatic space and yellow area indicates endolymphatic space. This case demonstrates endolymphatic hydrops in both the cochlea and vestibule.

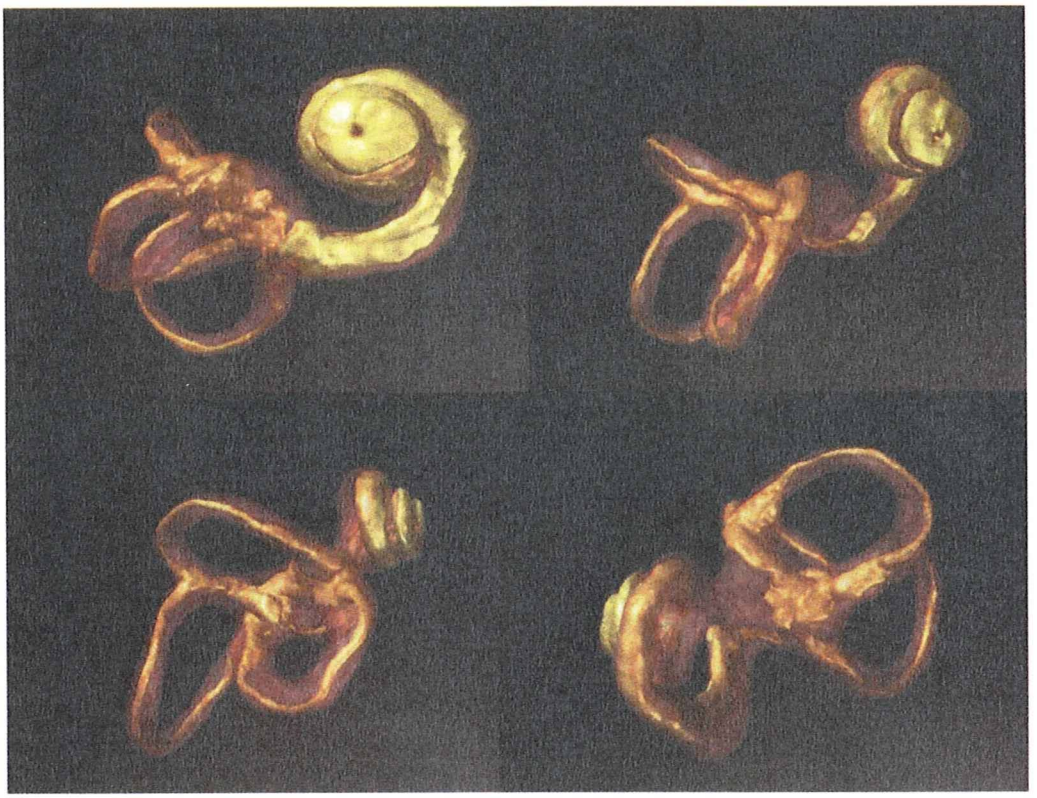

Figure 5. A 3D model of the inner ear of case 2 (with hydrops). Brown area indicates perilymphatic space and yellow area indicates endolymphatic space. This case demonstrates endolymphatic hydrops only in the cochlea.