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**ORIGINAL ARTICLE**

# Contrast enhancement of the inner ear after intravenous administration of a standard or double dose of gadolinium contrast agents

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**Abstract**

*Conclusion.* Imaging of the endolymphatic space was possible in most cases after administering a standard dose of gadolinium (Gd) by using heavily T2-weighted 3D fluid-attenuated inversion recovery (hT(2)W-3D-FLAIR) magnetic resonance imaging (MRI). *Objectives.* The aim of this study was to characterize the contrast enhancement in the inner ear after intravenous injection of Gd and to compare the signal intensity after a double dose or standard dose of Gd. *Methods:* We injected a standard dose of gadodiamide hydrate (DTPA-BMA) or a double dose of gadoteridol (HP-DO3A) intravenously in patients affected by Meniere's disease and performed hT(2)W-3D-FLAIR 3 T MRI. Contrast enhancement of the basal turn of the cochlea was evaluated semiquantitatively. *Results:* Endolymphatic hydrops was observed in the cochlea and vestibule of the affected ears of patients with Meniere's disease in both the double-dose group and the standard-dose group.

**Keywords:** *Contrast-enhanced MRI, intravenous injection, heavily T2-weighted 3D fluid-attenuated inversion recovery (hT(2) W-3D-FLAIR), Meniere's disease*

## Introduction

A method for endolymphatic space imaging by 3 Tesla (3 T) magnetic resonance (MR) after intratympanic injection of gadolinium (Gd) has recently been developed [1–7]. It gives useful information concerning the presence or absence of endolymphatic hydrops and the inner ear distribution of drugs such as steroids or gentamicin that are applied transtympanically.

We succeeded in obtaining endolymphatic space imaging by 3 T MR after intravenous injection of a double dose of gadoteridol (Gd HP-DO3A) [3]. Because administration of a double dose of intravenous Gd is not covered by the Japanese government health insurance system, except for use in the diagnosis of tumor metastases in the brain, an effective method of endolymphatic space imaging after an intravenous standard dose of Gd is essential so that endolymphatic space imaging can be widely clinically applied. More recently, we reported a new MR imaging (MRI) method that increases the sensitivity of a low concentration of Gd contrast by using optimized heavily T2-weighted 3D fluid-attenuated inversion recovery (hT(2)W-3D-FLAIR), which enables visualization of the endolymphatic space [8]. The advantages and disadvantages of intratympanic and intravenous injection of Gd are shown in Table I. Generally, contrast enhancement in the perilymph of the inner ear after intratympanic Gd injection was higher than that after intravenous Gd injection. Intratympanic injection gives very useful information, and the quantity of Gd contrast medium used is much less (about 0.5 ml of eightfold-diluted Gd) than that used in the intravenous injection method. However, patients must wait for a longer time after intratympanic injection before undergoing MRI (24 h) than

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Table I. Advantages and disadvantages of intratympanic and intravenous injection of gadolinium (Gd).

| Advantages of intratympanic method | Disadvantages of intratympanic method |
|---|---|
| Gd enhancement in the inner ear is high | Gd enhances inner ear only on the injected ear |
| Permeability of the round window can be evaluated | Gd distributes poorly in the inner ear under the poor permeability of the round window |
| Drug distribution inside the inner ear after intratympanic drug administration is predictable | Approval by the ethics review committee is necessary |
| **Advantages of intravenous method** | **Disadvantages of intravenous method** |
| Gd enhances inner ear in both ears | Poorer enhancement of the inner ear than in intratympanic method |
| The blood labyrinth barrier can be evaluated | Approval by the ethics review committee is necessary in double-dose administration |
| Distribution of the drug through the vessels in the inner ear can be imaged | Possible side effects (i.e. renal dysfunction), especially in double-dose administration |
| Approval by the ethics review committee is not required in case of standard-dose administration | |



after intravenous injection (4 h) because Gd distributes slowly in the inner ear through the round window. Intravenous injection can give information about the inner ears of both ears at the same time, but intratympanic injection gives information only for the injected side.

As we have reported previously, the signal intensity (SI) ratio also varied widely with intratympanic Gd injection [7]. This may be because of poor permeability of the round window by contrast agents in approximately 8–13% of the injected ears, caused by scarring due to otitis media, bony interference, a pseudomembrane around the round window or consolidation of the round window itself [9–12]. However, we can expect stable enhancement of the inner ear with the intravenous method. Tagaya et al. [13] reported that the correlation between endolymphatic hydrops and the permeability of the blood–labyrinth barrier indicated increasing permeability of the blood vessels with the progression of Meniere's disease. They reported that after intravenous Gd injection in Meniere's disease patients, the SI ratio of the affected ears was higher than that of the healthy ears. The SI ratio after intravenous Gd injection is a good indicator for the semiquantitative evaluation of disruption of the blood–labyrinthine barrier [13]. Blood–inner ear barrier pathological changes can only be demonstrated by intravenous injection of Gd rather than intratympanic injection of the contrast agent in animal models [14]. In the present study, we injected either a standard dose or a double dose of Gd intravenously in patients affected by Meniere's disease and performed 3 T MRI.

The aim of this study was to characterize the contrast enhancement in the inner ear after intravenous injection of Gd and, using the hT(2)W-3D-FLAIR method, to compare the signal intensity in the perilymph of a double dose and a standard dose of intravenous Gd.

## Material and methods

### *Patients*

Thirty-two patients with Meniere's disease (17 men, 15 women) who visited the Department of Otorhinolaryngology, Nagoya University Hospital, between April 2010 and December 2010 were enrolled in this study. Based on the criteria of the 1995 American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) [15], 6 patients had definite Meniere's disease, 9 patients had probable Meniere's disease, and 17 patients had possible Meniere's disease. All participants underwent intravenous Gd administration. Eleven patients (6 men, 5 women; mean age 48.5 years, range 20–64 years) were injected intravenously with gadoteridol (Gd HP-DO3A, ProHance; Eisai, Tokyo, Japan) and 21 patients (11 men, 10 women; mean age 59.0 years, range 19–79 years) were injected intravenously with gadodiamide hydrate (Gd DTPA-BMA, Omniscan; Daiichisankyo Pharmaceutical Co. Ltd, Tokyo, Japan). All patients gave written informed consent to participate in this study, which was attached to their electronic medical records. This study was approved by the ethics review committee of our university.

### *Intravenous Gd injection*

Patients underwent intravenous administration of Gd DTPA-BMA or Gd HP-DO3A, and 3 T MRI was performed 4 h after intravenous injection of the contrast agents. Although the standard doses of Gd DTPA-BMA and Gd HP-DO3A are 0.2 ml/kg, a

concentration of 0.4 ml/kg of Gd HP-DO3A is permitted by the Japanese government health insurance system if the aim is to visualize metastatic brain tumors. In the present study, a double dose (0.4 ml/kg) of Gd HP-DO3A or a standard dose (0.2 ml/kg) of Gd DTPA-BMA was injected intravenously.

*MRI*

Based on the results of previous studies [1–8], we used a scan delay of 4 h after intravenous Gd HP-DO3A or Gd DTPA-BMA injection to obtain strong signal in the inner ear. MRI scans were performed using a 3 T MR unit (Trio; Siemens, Erlangen, Germany) and a receive-only 32-channel phased-array coil. hT(2)W-3D-FLAIR MRI was performed as described previously [8]. T2-weighted 3D constructive interference in the steady state (CISS) imaging was performed to obtain reference images of labyrinthine fluid space anatomy. Since Gd injected intravenously enters the perilymph but not the endolymph, visualization of the endolymphatic space is possible. The degree of endolymphatic hydrops in the cochlea and vestibule was classified into three categories (none, mild or significant) according to previously reported criteria [15].

*Semiquantitative evaluation of contrast enhancement of Gd*

Contrast enhancement of the basal turn of the cochlea was evaluated semiquantitatively using hT(2)W-3D-FLAIR MRI after intravenous injection of Gd HP-DO3A or Gd DTPA-BMA. We next calculated the SI ratio. We used the SI of the cerebellum as a reference and determined the ratio between the SI of the affected basal turn of the cochlea and that of the cerebellum. We identified the position of the basal turn of the cochlea by referring to a T2-weighted 3D CISS image of the same slice. The results of this SI ratio measurement were reported to correlate well with those based on a quantitative method [16].

*Comparison between hearing level and SI ratio*

Correlation between averaged hearing level (dB) at 500, 1000, and 2000 Hz and SI ratio was investigated in the standard-dose and double-dose groups.

*Statistical analysis*

Differences in the SI ratio between the double-dose group and the standard-dose group were evaluated with a Mann-Whitney *U* test. The age distribution in each group and other categorical variables were evaluated with the *t* test and $\chi^2$ test, respectively. Correlation between hearing level and SI ratio was investigated by Spearman's correlation coefficient. $P < 0.05$ was defined as the level of significance.

## Results

Figure 1 shows images taken using conventional 3D-FLAIR and hT(2)W-3D-FLAIR. after intravenous injection of the standard dose of Gd. We obtained more information about the inner ear by using hT(2)W-3D-FLAIR than by using conventional 3D-FLAIR.

Figure 2 shows hT(2)W-3D-FLAIR MRI taken 4 h after intravenous double-dose (Figure 2A, B) and standard-dose (Figure 2C, D) Gd injection. In Figure 2A and B, bilateral endolymphatic hydrops was recognized in the cochlea and the vestibule of a patient in the double-dose group with bilateral Meniere's disease. In Figure 2C and D, significant endolymphatic hydrops was observed in the cochlea and vestibule of the affected ear of a patient in the standard-dose group with unilateral Meniere's

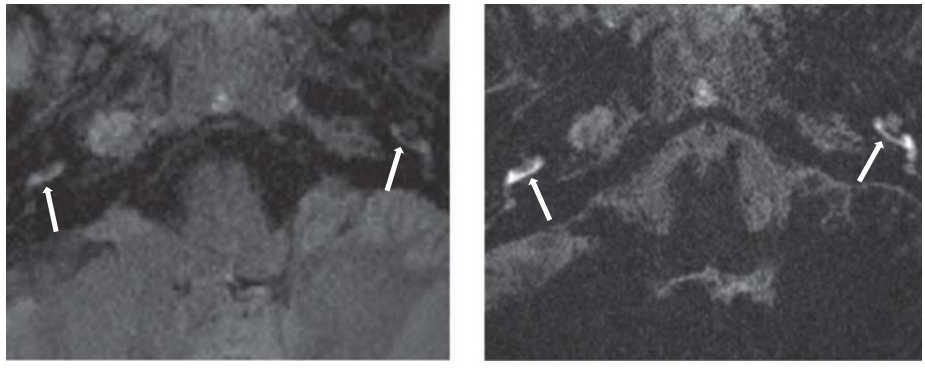

Figure 1. Images of the same slice of the basal turn of the cochlea enhanced after injection of the standard dose of Gd. The left image was taken using conventional 3D-FLAIR and the right image was taken using hT(2)W-3D-FLAIR. We obtained more information about the inner ear by using hT(2)W-3D-FLAIR than by using conventional 3D-FLAIR.

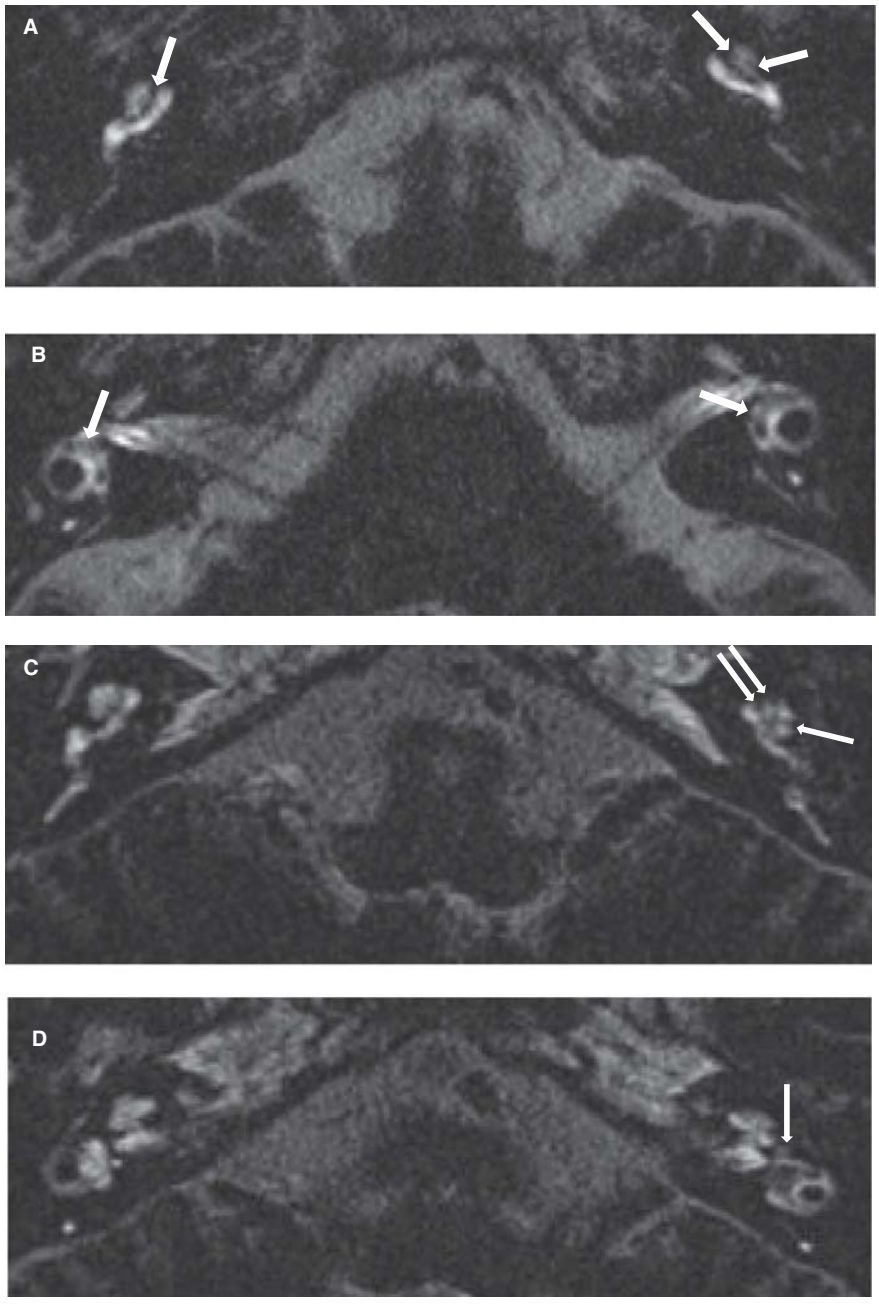




Figure 2. hT(2)W-3D-FLAIR MRI taken 4 h after intravenous double-dose (A, B) and standard-dose (C, D) Gd injection. (A, B) A 64-year-old female patient with bilateral Meniere's disease. (A) Endolymphatic hydrops was recognized in the cochlea of both ears (arrows). (B) Significant endolymphatic hydrops was recognized in the vestibules of both ears (arrows). (C, D) A 43-year-old male patient with unilateral Meniere's disease in the left ear. (C) Significant endolymphatic hydrops was recognized in the left cochlea. (D) Significant endolymphatic hydrops was recognized in the left vestibule (arrow).

disease. In the double-dose group, all 11 patients showed endolymphatic hydrops in either the cochlea or the vestibule in at least one ear. In the standard-dose group, 20 of 21 patients showed endolymphatic hydrops in either the cochlea or the vestibule in at least one ear; in the remaining patient, the presence or absence of endolymphatic hydrops was impossible to judge because of the weak signal. Therefore, further imaging analysis of the degree of endolymphatic hydrops and the SI ratio in the inner ear was performed on 20 patients in the standard-dose group.

In terms of grading the endolymphatic hydrops in 22 ears of the double-dose group, 9 ears had none, 1 ear had mild endolymphatic hydrops, and 12 ears had significant endolymphatic hydrops in the cochlea, while 6 ears had none, 1 ear had mild endolymphatic

Table II. Patients' clinical and imaging characteristics.

| Parameters | Double-dose group | Standard-dose group | *p* Value* |
|---|---|---|---|
| No. of patients | 11 | 21 | |
| Age (average ±SD) | 48.5 ± 13.1 | 59.0 ± 15.8 | 0.064 |
| Gender | Male 6, female 5 | Male 11, female 10 | 0.981 |
| Number of ears with cochlear hydrops (none or mild, significant) | 10, 12 | 23, 17 | 0.363 |
| Number of ears with vestibular hydrops (none or mild, significant) | 7, 15 | 23, 17 | 0.053 |
| Diseased ears with Meniere's disease | 16 | 27 | 0.669 |
| Contralateral ears with unilateral Meniere's disease | 6 | 13 | |

*$t$ test for age and $\chi^2$ test for other parameters.



hydrops, and 15 ears had significant endolymphatic hydrops in the vestibule. In 40 ears in the standard-dose group, 18 ears had none, 5 ears had mild endolymphatic hydrops, and 17 ears had significant endolymphatic hydrops in the cochlea, while 9 ears had none, 14 ears had mild endolymphatic hydrops, and 17 ears had significant endolymphatic hydrops in the vestibule.

The contrast effects of Gd are stronger in the diseased ears than in the contralateral ears of patients with unilateral Meniere's disease, which reflects the impaired blood–labyrinth barrier, as previously reported. Furthermore, this impairment is associated with higher grades of endolymphatic hydrops [13]. Table II shows the MRI characteristics of the two groups. The number of ears with significant endolymphatic hydrops and the number with no or mild hydrops in the cochlea did not differ significantly between the double-dose group and the standard-dose group. The difference in the incidence of hydrops in the vestibule between the two groups is close to, but still does not reach a level of significance. The number of diseased ears in patients with Meniere's disease and that of contralateral non-diseased ears in patients with unilateral Meniere's disease are not significantly different between the double-dose group and the standard-dose group.

To evaluate the contrast enhancement of Gd, we selected the bright area of the basal turn of the cochlea that was contrasted (Figure 3). A high SI ratio indicates that the contrast enhancement of the basal turn of the cochlea is strong. The SI ratio ranged from 9.7 to 29.1 (mean ± SD = 18.3 ± 5.2) in the double-dose Gd group and from 6.1 to 30.0 (mean ± SD = 12.5 ± 5.0) in the standard-dose Gd group. A significant difference in the SI ratio was observed between the double-dose group and the standard-dose group ($p < 0.01$) (Figure 4).

No correlation between averaged hearing level (dB) at 500, 1000, and 2000 Hz and SI ratio was found in the diseased ears and non-diseased ears of the standard-dose group ($p = 0.21$ and $p = 0.99$). Likewise, no correlation between averaged hearing level at the three frequencies and SI ratio was observed in the diseased ears and non-diseased ears of the double-dose group ($p = 0.28$ and $p = 0.21$).

## Discussion

The present study demonstrated that the SI ratio in the inner ear after intravenous injection of double-dose Gd is higher than that after standard-dose Gd injection. Factors that influence the SI ratio in the inner ear, i.e. the degree of endolymphatic hydrops and the ratio of diseased ears, did not differ significantly between the two groups. No correlation between hearing level and SI ratio was found in the two groups.

Gd DTPA-BMA and Gd HP-DO3A are commonly used as MR contrast agents. Gd DTPA-BMA is based

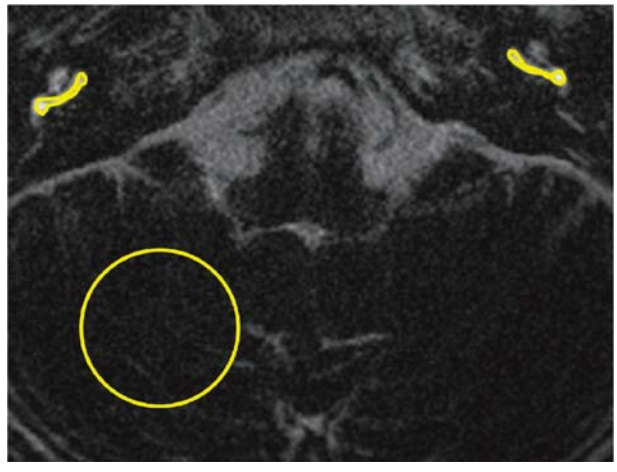

Figure 3. An example of the region of interest (ROI) on a contrast-enhanced hT(2)W-3D-FLAIR image. The ROI for cochlear fluid signal intensity (SI) measurement was drawn manually around the basal turn of the cochlea. The circular ROI for SI measurement of the cerebellum was positioned in the most artifact-free area of the cerebellum. Finally, we compared the SI ratio between the basal turn of the cochlea and the cerebellum.

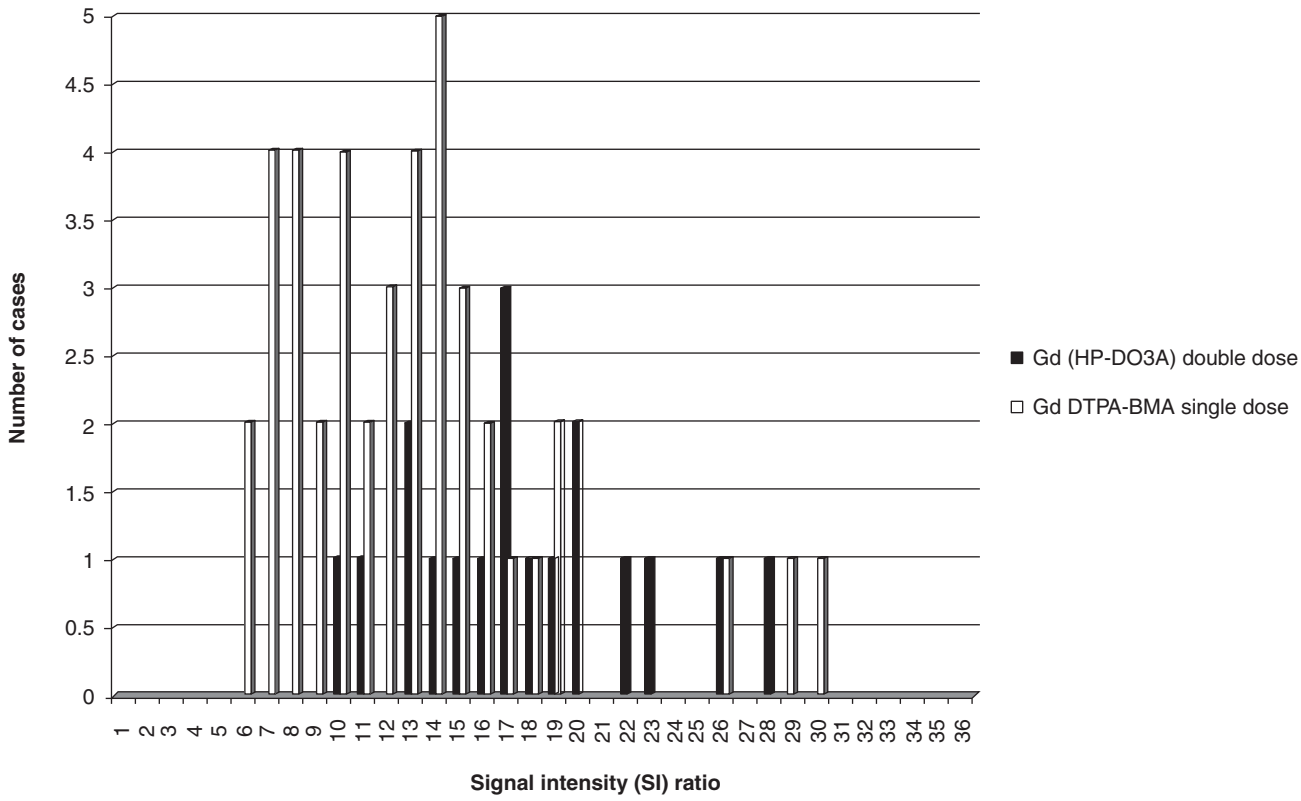


Figure 4. Comparison of the signal intensity (SI) ratio of enhanced hT(2)W-3D-FLAIR MRI between double-dose Gd and standard-dose Gd. The SI ratio ranged from 9.7 to 29.1 (mean ± SD = 18.3 ± 5.2) in the double-dose group and from 6.1 to 30.0 (mean ± SD = 12.5 ± 5.0) in the standard-dose group.

on the linear triamine and Gd HP-DO3A is based on the macrocyclic tetra-amine framework. Both Gd DTPA-BMA and Gd HP-DO3A are nonionic chelates (total charge of 0) [17]. The molecular weight of Gd-DTPA-BMA is 646 and that of Gd HP-DO3A is 559. Imaging of the endolymphatic space by 3 T MR after intravenous injection of Gd was first obtained after injection of a double dose of Gd HP-DO3A. A double dose of Gd HP-DO3A is permitted by the Japanese government health insurance system for the investigation of metastatic brain tumors, but this dose is not approved for investigation of the inner ear. In this study, we used the hT(2)W-3D-FLAIR method. Naganawa et al. reported that hT(2)W-3D-FLAIR increases the sensitivity of detection of low-concentration Gd and enables better visualization of the endolymphatic space than conventional 3D-FLAIR [8]. We were able to obtain more information about the inner ear by using hT(2)W-3D-FLAIR than by using conventional 3D-FLAIR (Figure 1). Thus, although a double dose of Gd gives more information than a standard dose of Gd, it was possible in most cases in this study (20 of 21 patients) to determine the existence of endolymphatic hydrops with a standard dose of Gd using hT(2)W-3D-FLAIR.

In conclusion, hT(2)W-3D-FLAIR was able to facilitate imaging of the endolymphatic space after intravenous injection of the standard dose of Gd.

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

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