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内外リンパ腔画像からみた内耳疾患の病態と局所療法

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総合研究報告書

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研究要旨

MRIによる内リンパ腔の描出において、3D-real inversion recovery (IR) というソフトの開発、32チャンネルヘッドコイルの導入などにより内リンパ水腫をより鮮明に画像化できるようになった。この方法を用いて、内耳疾患の臨床症状と画像所見の関係について、様々な観点から検討した。今まで、内リンパ腔の描出のためには、ガドリニウム造影剤を鼓室に注入する必要があったが、ガドリニウム造影剤を静脈に投与しても内リンパ水腫の画像化ができることを示した。ガドリニウム造影剤の鼓室内投与法と静脈内投与法の長所、短所について検討した。

A．研究目的

内耳は、側頭骨の中の小さくて繊細な器官であり、内リンパ腔の画像化は困難であった。本研究では、内リンパ腔の画像化を臨床的に充分応用できるようにするとともに、臨床症状と画像所見との関係を調べ、内耳病態の解明に貢献しようとした。また、内リンパ腔の画像化においてはガドリニウム造影剤を鼓室内か静脈内に投与するが、Drug delivery system の観点から内耳への薬剤投与法について検討した。

B．研究方法

3テスラMRI装置を用いて3D-FLAIRのほかに3D- real IR 法でも内耳画像を撮った。120例にガドリニウム造影剤を8倍、もしくは16倍に生食でうすめて鼓室内注入し24時間後にMRI撮影を行った。また、静脈内にガドリニウム造影剤を通常の倍量（0.4mL/kg）もしくは通常量(0.2mL/kg)静注し4時間後にMRI撮影を行った。

（倫理面への配慮）

ガドリニウム造影剤の鼓室内投与、造影剤倍量静脈内投与については、名古屋大学医学部倫理委員会の承認を得てから行った。なお、造影剤倍量静脈内投与は、転移性脳腫瘍では保険で認められている量である。

C．研究結果

ガドリニウム造影剤の鼓室内投与では、16倍希釈は、8倍希釈と比べて造影効果が弱かった。その造影効果は個人差が大きいが、鼓室内16倍希釈と静脈内倍量投与とほぼ同様であった。ガドリニウム造影剤の鼓室内投与では、今まで1例も副作用を認めていない。鼓室内投与では8倍希釈が適当と判断した。内リンパ腔描出におけるガドリニウム造影剤の鼓室内投与と静脈内投与の長所、短所を表にまとめた。

表　MRIによる内リンパ腔描出における造影剤投与法

	長所	短所
鼓室内投与	●内耳造影効果が高い ●正円膜の透過性がわかる ●ステロイドやゲンタマイシンなど鼓室内薬剤投与法に有用な情報	●一側のみ。両側調べるには両側に造影剤注入必要 ●正円窓の透過性が悪いと判読不能または不明 ●造影剤のオフラベル使用。倫理委員会許可必要
静脈内投与	●両側内耳が評価できる ●血液迷路関門の状態がわかる ●薬物を静脈内投与したときの内耳への移行状況に有用な情報 ●造影剤通常量で内リンパ腔を評価できれば、倫理委員会の許可不要	●内耳造影効果が弱い ●造影剤倍量投与では倫理委員会許可必要 ●全身への副作用に注意必要

臨床症状と内リンパ画像所見との関連では、内リンパ水腫は症状の変化とともに水腫の程度が変化すること、いわゆる蝸牛型メニエール病においても蝸牛だけでなく前庭にも水腫が存在すること、遅発性内リンパ水腫対側型でも、画像では両側に水腫がある例があること、VEMP は前庭の水腫、蝸電図は蝸牛の水腫とより関係が強いことなどを明らかにした。

D．考察

いわゆる蝸牛型メニエール病では、聴力の変動はあるのにめまいが起こらないが、内耳画像検査では、蝸牛だけでなく前庭にも水腫が存在することがわかった。メニエール病のめまい発作の出現に球形嚢と蝸牛をつなぐ結合管の状態が関与するという考え方が提唱されている。最近、我々は、撮影された内耳 MRI から結合管が開いているかどうか画像化することができた。今後、この結合管や球形嚢と卵形嚢をつなぐ管の状態も検討し臨床症状との関係を検討していく予定である。

本臨床研究では、ミネソタ大学の側頭骨標本をコンピュータにいれ立体モデルを作成した。そのモデル作性においても内リンパ水腫が強く、拡大した球形嚢の内リンパ腔が結合管を覆うようになると、結合管の状況がわかりにくかった。結合管の画像評価は、困難な面があるが、臨床症状との関連で重要であり今後の課題としたい。

E．結論

MRI のソフトの開発や新しいハードの導入によって、より良い内リンパ腔の画像化が可能になった。この画像を用いて臨床所見・検査所見との関連について新しい治験を得ることができた。内耳 MRI は、結合管の画像化など、今後さらに進歩すると確信している。

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総合研究報告書

内外リンパ腔から画像からみた内耳疾患の病態

研究要旨

内外リンパ腔画像のMR技術開発により安定化と高精度化をはかった。real IRにより内リンパ、骨、外リンパの3者を分離して、理解しやすい画像を取得することに世界ではじめて成功した。静注Gdによる内外リンパ分離や内外リンパ腔分離立体表示など従来不可能であったことを可能とした。また薄い濃度でも内外リンパ腔の分離ができるようなパルスシークエンスソフトの開発を行った。

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A．研究目的

MRI により迷路内外リンパ分離描出を簡便に多くの施設で可能とし、さらに高精度化、3次元化、低侵襲化するための技術開発をおこなう。つまりハードとともに、時間効率、コントラスト、空間分解能を向上させたパルスシークエンスソフトの開発も行なう。

B．研究結果

最終的には、32チャンネルコイルと3D-real IR法を用いることによって3次元的に内外リンパ腔を分離描出可能となった。0.4mm x 0.4mm x 0.8mmという従来では考えられない高分解能画像を高コントラストで取得できた。それによりメニエール病による内リンパ水腫が立体的に観察可能となった。また定量の可能性も見えてきた。さらに静注4時間後でも内外リンパの分離が可能になりつつある。このreal IRにより画像非専門家でも内リンパ水腫評価が容易となった。

C．考察

3年間の開発の中でやはり32チャンネルコイルの貢献度は大きかった。また静注での検出を可能とする現在開発中の方法にも期待がもてる。一種の形態診断であるが、従来までそれすらできなかった分野においては形態診断でも十分に新規性がある。

D．結論

コイルやパルスシークエンスソフトの開発により内外リンパ腔画像の高精度化が実現した。さらなるソフト、ハードの開発をめざして、内リンパの詳細解剖を明らかにしたい。7Tでの内耳撮影も国際的に協力して開発を開始したところである。さらなる内耳疾患の病態解明につながると思われる。

研究成果の刊行に関する一覧表

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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

positive if the negative signal area on 3D-real IR in the vestibule is more than a quarter of the entire vestibule. These tentative criteria were established based on previous histological research in humans and animals [13–15].

Results

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-real IR. The low signal area of surrounding bone on 3D-FLAIR showed near zero signal on 3D-real IR (Figs. 1, 2, 3). Gd-containing perilymphatic space showed high signal on 3D-real IR images. The spatial relationship between endolymphatic space and perilymphatic space can be well appreciated on 3D-real IR images. In nine Meniere's disease patients and two patients with acute low-tone sensorineural hearing loss, the endolymphatic space was enlarged. In the two patients with acute low-tone sensorineural hearing loss, endolymphatic space in the upper turn of the cochlea seemed to be more enlarged, while perilymphatic space of the scala vestibuli seemed to be narrower compared to that of the lower turn. In two cases of delayed endolymphatic hydrops, both the left and right ears showed endolymphatic hydrops.

No side effect relating to intratympanic administration of Gd-DTPA was observed.

Discussion

Separate visualization of perilymph and endolymph fluid space by MR imaging has been tried by several researchers [16]. Direct visualization of Reissner's membrane using high spatial resolution imaging was successful in animals [17] and human cadavers [18, 19]; however, clear visualization in living human subjects has not been successful due to the limited spatial resolution of clinical MR imaging units [20, 21].

Intravenous administration of Gd-DTPA in healthy human volunteers resulted in a slight signal increase in the labyrinth after 4 h [22]. However, the separation between the endolymphatic space and perilymphatic space was not clear, probably due to an insufficient concentration of Gd in the perilymphatic space.

Intratympanic injection of Gd-DTPA and the utilization of 3D FLAIR at 3 T made the visualization of endolymphatic hydrops possible in vivo [2]. Intratympanically administered Gd-DTPA distributed mainly into perilymphatic fluid space, and not into endolymphatic space. However, it was difficult to differentiate the low signal of endolymphatic space on 3D FLAIR from surrounding bone. Especially endolymphatic space in the vestibule is difficult to delineate when it is enlarged [2].

To delineate endolymphatic space precisely and to allow the quantification of endolymphatic-space volume in the future, endolymphatic space needs to be visualized separately, not only from perilymphatic space, but also from bone and air. By changing the inversion time, endolymphatic space and perilymphatic space might be separately visualized as positive signal. This will allow the volume quantification of each space in the future.

Quantification of each space is an important goal in the future for the objective diagnosis of endolymphatic hydrops and for monitoring treatment efficacy. Even with current spatial resolution however, it will take 30 min to

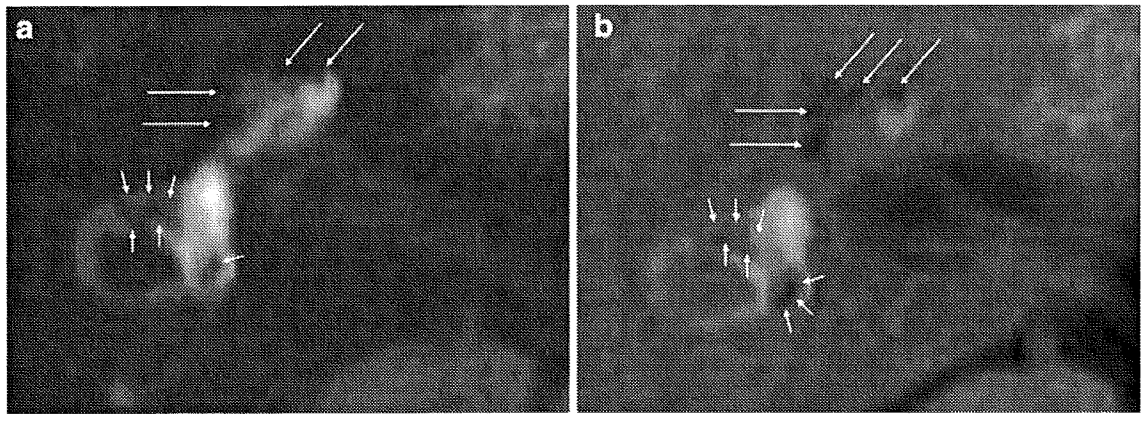

Fig. 1 A 31-year-old man with acute low-tone senrorineural hearing loss in the right ear (average, 31 dB). All images were obtained 24 h after the intratympanic injection of Gd-DTPA. (**a**) 3D-FLAIR (9,000/134/2,500) shows enlarged endolymphatic space in the cochlea (arrows) as low signal areas; however, the boundary between endolymphatic space and surrounding bone is unclear. Mild enlargement of the endolymphatic space in the vestibule (short arrows) is observed. (**b**) A 3D-real IR sequence (9,000/134/1,700) visualizes severely enlarged endolymphatic space in the cochlea (arrows) and mildly enlarged endolymphatic space in the vestibule (short arrows) as negative signal intensity values, while the surrounding bone area has near zero signal intensity. This image allows the separation of perilymph space (high signal intensity), endolymph space and surronding bone on a single image. In this acute low-tone senrorineural hearing loss patient, perilymphatic space in the upper cochlear turn seems to be narrower than in the lower turn due to relatively severe endolymphatic hydrops in the upper turn

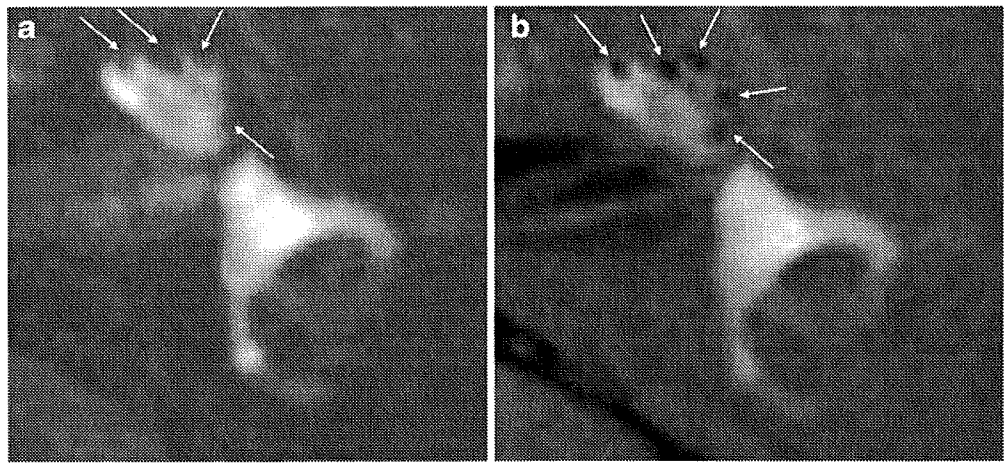

Fig. 2 A 33-year-old man with delayed endolymphatic hydrops. All images were obtained 24 h after the intratympanic injection of Gd-DTPA. (**a**) 3D-FLAIR (9,000/134/2,500) shows enlarged endolymphatic space in the cochlea (arrows), but not in the vestible. The boundary between endolymphatic space and surrounding bone is unclear. (**b**) A 3D-real IR sequence (9,000/134/1,700) visualizes severely enlarged endolymphatic space in all cochlear turns (arrows) as negative signal intensity values, while the surrounding bone area has near zero signal intensity. This image makes possible the delineation of the scala media (negative signal intensity; black on this image) from perilymph space (scala tympani and scala vestibuli with positive high signal intensity; white on this image) and surronding bone (near zero signal; gray on this image) on a single image

obtain both endolymphatic images and perilymphatic images separately. Furthermore, the spatial relationship between the two spaces cannot be appreciated without the fusion of two separately obtained images. Non-uniform distribution of Gd-DTPA in the perilymphatic space also would make it difficult to uniformly suppress the signal of perilymphatic fluid with a single inversion time.

The present method with 3D inversion recovery using real reconstruction divides the signal magnitude of the endo- and perilymphatic fluid into positive and negative; thus, the precise value of the inversion time is not as important.

One of the limitations of the present method is the relatively low spatial resolution in the slice direction due to limited scan time and signal-to-noise ratio. To improve the signal-to-noise ratio, further study is necessary to investigate strategies that reduce acquisition time (and improve imaging efficiency), such as shorter TR and longer echo-train length. A shorter acquisition time would allow us to obtain higher spatial resolution or a larger number of excitations.

Another limitation of this study is the lack of histological confirmation for the presence of endolymphatic hydrops. It is virtually impossible to obtain histological proof in human

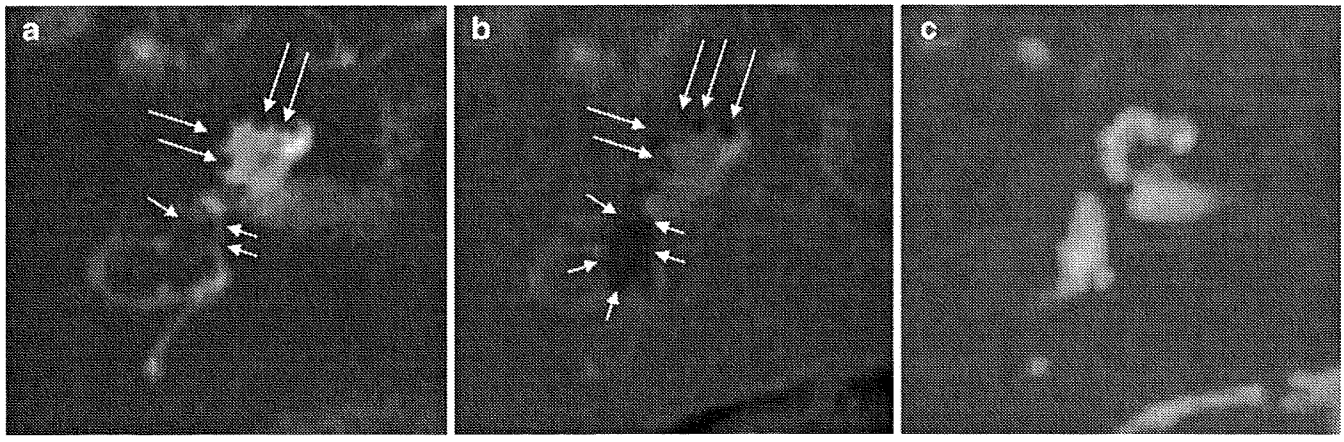

Fig. 3 A 42-year-old man with Meniere's disease. All images were obtained 24 h after the intratympanic injection of Gd-DTPA. (**a**) 3D-FLAIR (9,000/134/2,500) shows severely enlarged endolymphatic space in the cochlea (arrows) and in the vestibule (short arrows). The boundary between endolymphatic space and surrounding bone is unclear. (**b**) A 3D-real IR sequence (9,000/134/1,700) visualizes severely enlarged endolymphatic space in all cochlear turns (arrows) and in the vestibule (short arrows) as negative signal intensity values, while the surrounding bone area has near zero signal intensity. (**c**) 3D-CISS (11.42/5.71/flip angle 50 degree) image shows the combination of endolymphatic and perilymphatic space