MAJOR PAPER

Heavily T_2-Weighted 3D-FLAIR Improves the Detection of Cochlear Lymph Fluid Signal Abnormalities in Patients with Sudden Sensorineural Hearing Loss

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Purpose: To compare the signal increase in cochlear lymph fluid on three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) in patients with sudden sensorineural hearing loss (SNHL) between regular contrast 3D-FLAIR (FL) and heavily T_2-weighted 3D-FLAIR (HF).

Methods: Twenty-five patients with unilateral sudden SNHL and eight healthy volunteers were included. Patients were divided into two groups: the mild group consisted of 9 patients, with an average hearing level of 60 dB or less; the severe group consisted of 16 patients, with an average hearing level of more than 60 dB. All patients and healthy volunteers underwent magnetic resonance (MR) cisternography for anatomical reference of the fluid space with FL and HF at 3 T. The region of interest (ROI) was manually drawn on the mid-modiolar section of the MR cisternography around the cochlea. The ROI for noise was drawn within the air space. ROIs were copied onto the FL and HF images. The contrast-to-noise ratio (CNR) between the affected and non-affected ear was measured in the patient group and the CNR between the right and left ear was also measured in the control group. Differences in the CNR on FL and HF images among the three groups were tested by one-way analysis of variance (ANOVA).

Results: There was a statistically significant difference in mean CNR on HF among the three groups ($P < 0.001$). Furthermore, based on pairwise comparisons, there was a statistically significant difference between them in mean CNR on HF ($P < 0.05$). There was no statistically significant difference in mean CNR on FL among the three groups ($P = 0.074$).

Conclusions: HF is more sensitive to signal alterations in cochleae with sudden SNHL than FL.

Introduction

A signal increase in cochlear lymph fluid on three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) in patients with sudden sensorineural hearing loss (SNHL) was first reported 10 years ago.[1] After this initial report, several additional reports have been published.[2–7]

Clinical values of this signal increase on 3D-FLAIR have been discussed in a recently published meta-analysis.[8] High signal on 3D-FLAIR was reported to be detected in 95 out of 249 patients (38.1%). The degree of hearing loss was reported to be more severe in ears with high signal on 3D-FLAIR. Moreover, the existence of high signal on 3D-FLAIR was associated with a 2.88 times greater incidence of vertigo. Meta-analysis of the hearing recovery rate showed the chance of recovery in the high signal group was significantly less than in the no signal group.

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A recent study reported that the signal increase within the inner ear was not detected in any ears on "regular contrast" non-contrast material enhanced 3D-FLAIR in ears with mild sudden SNHL (defined as a hearing level no greater than 60 dB). In contrast, the signal increase was detected in 2 of 6 ears with severe sudden SNHL (defined as a hearing level greater than 60 dB).[9]

Heavily T_2-weighted 3D-FLAIR (HF) has been reported to be more sensitive to subtle T_1-changes in fluid than regular contrast 3D-FLAIR (FL).[10,11] Pulse sequence parameters of HF have been optimized for the evaluation of fluid signal change with longer T_2 value rather than for the evaluation of brain parenchyma.[10] For the visualization of endolymphatic hydrops in the inner ear, FL requires intratympanic administration of gadolinium-based contrast agent[12] or a double dose of intravenously administered gadolinium-based contrast agent.[13] In contrast, HF enables the detection of endolymphatic hydrops after a single dose of intravenous gadolinium-based contrast agent in patients with Ménière's disease.[14–23]

In a non-contrast material enhanced study of the inner ear for the detection of lymph fluid abnormalities in patients with sudden SNHL, we had employed both FL and HF in routine clinical practice. The purpose of this retrospective study was to compare the signal of cochlear lymph fluid on FL and HF in ears with sudden SNHL.

Materials and Methods

Patients

Between January 1, 2013 and January 31, 2015, 25 patients (age 6–77, 14 males, 11 females) with unilateral sudden SNHL underwent non-contrast enhanced magnetic resonance (MR) imaging of the inner ear including FL and HF at 3 Tesla.

Images from eight healthy male volunteers were included for comparison as controls; these were scanned using the same imaging protocol as for the SNHL patients. Details of the patients and volunteers are listed in Table 1.

In our hospital, patients with sudden SNHL are routinely ordered to undergo MR examination at their first visit. Some patients who were referred from other hospitals, however, had already undergone MR imaging. For those patients referred from other hospitals, MR imaging is not performed in our hospital during the acute phase, and is scheduled for weeks or months later.

The diagnostic criteria for sudden SNHL used in this study were that the patient could describe the day of onset of sudden SNHL, which had no obvious cause, and that no hearing loss (HL) had been noted before the onset of SNHL. We excluded patients with fluctuating HL or progressive HL. The purpose of MR imaging for sudden SNHL in our hospital is to rule out vestibular

schwannoma by MR cisternography and to assess signal alterations of the labyrinthine fluid by FL and HF.

The medical ethics committee of our institution approved the study of healthy volunteers and written informed consent was obtained from all volunteers prior to performing the scans. For the retrospective study of SNHL patients, the medical ethics committee of our institution approved this retrospective study with a waiver of written informed consent from the patients.

Hearing Level Test

Hearing levels were evaluated using an audiometer (Model AA-79S; Rion Co. Ltd., Kokubunj, Tokyo) in a sound-insulated chamber. The initial audiograms were obtained at the first visit, and the final audiograms were taken more than 2 months after the first visit, except for patients who recovered completely within this period. In some patients from other hospitals, initial audiograms were obtained more than 2 weeks later from onset. The average hearing level was expressed as the weighted average score at four frequencies (500, 1000, 2000, and 4000 Hz) as shown below:

$$\text{Average hearing level} = (500\text{ Hz} + 2 \times 1000\text{ Hz} + 2 \times 2000\text{ Hz} + 4000\text{ Hz})/6$$

If the patient did not respond to the maximum sound level produced by the audiometer, we defined the threshold as 5 dB added to the maximum level.

The outcome of sudden SNHL was categorized as positive improvement or negative improvement. The average hearing level recovery was ranked as either negative (improvement in hearing of less than 30 dB on average) or positive (improvement in hearing of 30 dB or more on average or improvement to the same degree of hearing as in the contralateral ear). The prognosis of hearing recovery was assigned as y = yes for recovery or n = no recovery.

Patients were divided into two groups according to average hearing level at the first visit: a mild group, with an average hearing level of 60 dB or less; and a severe group, with an average hearing level of more than 60 dB.

MR Imaging

All MR imaging was performed on a 3 Tesla scanner (Verio, Siemens, Erlangen, Germany) using a 32-channel array head coil. All patients and healthy volunteers underwent heavily T_2-weighted MR cisternography for anatomical reference of the fluid space, and regular contrast 3D-FLAIR (FL) and hT₂w-3D-FLAIR (HF) according to the clinical protocol of our hospital for evaluating labyrinthine fluid alterations.[1,5,7,8] All scans utilized a 1-mm identical slice thickness. Parameters were set according to previously reported studies.[11,19,21] Detailed scan parameters are shown in Table 2.

Table 1. Summary of volunteers and patients

	Group	Age	Gender	Onset to MR (days)	Hearing level of right ear (dB)	Hearing level of left ear (dB)	Affected side	Recovery of hearing loss (yes or no)	CNR of cochlea on 3D-FLAIR (CNR-FL)	CNR of cochlea on hT$_2$-FLAIR (CNR-HF)
1		50	m						0.5	–0.4
2		53	m						–0.1	0.2
3		31	m						0.5	–0.2
4	Volunteers	30	m		N.A.				0.2	0.3
5		36	m						0.5	0.1
6		38	m						0.4	0.1
7		42	m						0.3	0.5
8		29	m						–0.1	0.5
	Average	38.6							0.3	0.1
	SD	9.1							0.3	0.3
1		56	m	1	16.7	52.5	L	y	0.0	1.9
2		70	m	24	60.0	22.5	R	y	1.0	3.2
3		68	f	24	23.3	53.3	L	n	–0.9	1.7
4	Mild hearing loss	65	m	57	55.8	45.8	R	n	0.4	1.2
5		33	m	2	31.7	10.0	R	y	0.3	2.9
6		25	f	134	36.7	10.8	R	n	–0.9	1.8
7		77	f	17	46.7	18.3	R	y	0.5	1.3
8		63	m	16	19.2	44.2	L	n	–0.3	1.0
9		63	m	5	21.7	41.7	L	y	–0.3	0.6
	Average	57.8		31.1					0.0	1.7
	SD	17.4		42.2					0.6	0.8
1		43	m	38	61.7	20.0	R	y	–0.2	2.0
2		6	m	70	12.0	113.3	L	n	–0.5	2.1
3		36	m	38	11.7	77.5	L	y	–0.2	2.9
4		64	f	104	77.3	35.0	R	n	1.2	3.2
5		35	f	114	16.7	77.3	L	n	3.3	5.8
6		75	f	6	80.8	15.0	R	y	0.2	2.4
7		54	m	5	90.8	17.5	R	y	5.1	3.6
8	Severe hearing loss	55	m	20	15.0	83.3	L	n	0.7	3.4
9		34	m	8	88.3	14.2	R	y	0.7	5.3
10		65	f	5	34.2	65.0	L	y	–0.3	1.3
11		76	f	71	19.2	73.3	L	n	0.3	1.6
12		8	f	75	10.0	67.5	L	n	4.9	5.6
13		63	f	48	81.7	25.8	R	n	0.7	2.7
14		49	m	30	13.3	105.0	L	n	1.5	1.7
15		13	f	18	15.0	82.5	L	n	–0.5	3.0
16		64	m	4	80.8	16.7	R	n	2.6	5.7
	Average	47.4		31.0					1.2	3.3
	SD	24.0		27.5					1.8	1.5

CNR: contrast-to-noise ratio of cochlear fluid signal between the right and left sides in volunteers and affected and non-affected sides in sudden sensorineural hearing loss patients. Negative values are allowed. f, female; FL, regular contrast 3D-FLAIR; FLAIR, fluid attenuated inversion recovery; HF: heavily T$_2$-weighted 3D-FLAIR; L, left; m, male; MR: magnetic resonance; n, no; R, right; SD: standard deviation; y, yes.

Table 2. Pulse sequence parameters

Sequence name	Type	Repetition time (ms)	Effective echo time (ms)	Inversion time (ms)	Flip angle (degree)	Section thickness (mm)	Pixel size (mm)	Number of slice	Echo train length	Field of view (mm)	Number of excitation	Scan time (min)
MR cisternography for volunteers (MRC-v)	SPACE with restore pulse	4400	544	NA	90/initial 180 decrease to constant 120	1	0.5×0.5	104	173	150×180	1.8	3
MR cisternography for patients (MRC-p)	CISS	6.6	3.3	NA	50	1	0.5×0.5	104	1	150×180	1	4
Heavily T_2-weighted 3D-FLAIR (HF)	SPACE with inversion pulse	9000	544	2250	90/initial 180 decrease to constant 120	1	0.5×0.5	104	173	150×180	2	6
3D-FLAIR (FL)	SPACE with inversion pulse	9000	457 (contrast equivalent to 117)	2500	90/variable (average 120)	1	0.5×0.5	96	119	150×180	2	6

Parallel imaging technique (GRAPPA) is utilized for all sequences except CISS. MRC-v and HF utilize frequency selective fat suppression pre-pulse, and MRC-v utilizes restore magnetization pulse at the end of echo train. Each 3D slab is set in an identical axial orientation. 3D-FLAIR, three-dimensional fluid-attenuated inversion recovery; CISS, constructive interference in steady-state; MR, magnetic resonance; NA, not applied; SPACE, sampling perfection with application-optimized contrasts using different flip angle evolutions.

Image Analyses

Images were quantitatively evaluated on a PACS viewer (Rapideye, Toshiba Medical Systems, Tokyo) by a neuroradiologist with 26 years of experience in the field of clinical MRI. Lymph fluid signal measurements were performed for the cochlea.[24]

For the cochlear ROI, the slice where the cochlear modiolus is visually largest was selected. If two or more slices showed a comparable modiolar size, the slice with the largest modiolar height was chosen. When contouring the cochlea on the MR cisternography, the modiolus was excluded (Fig. 1).

For quantitative evaluation of the patients, the contrast-to-noise ratio (CNR) between the affected and unaffected cochleae was measured for both FL and HF images. For evaluation of the volunteers, the CNR between the right and left cochleae was measured. For CNR, negative values are allowed. Noise level was defined as the standard deviation (SD) of the air space signal in the lower corner of the image. The ROI for noise quantification was drawn as a circular ROI with a diameter of 10 mm. The cochlear ROIs and noise ROIs were then copied from the MR cisternography onto the FL and HF images. The CNR was defined as the difference in signal intensity value between both cochleae divided by the SD of the air signal. The average CNR from the FL and HF images were compared. CNR was defined as follows:

For patients: (signal intensity of cochlear ROI of affected side – unaffected side)/SD of noise

For volunteers: (signal intensity of cochlear ROI of right side – left side)/SD of noise
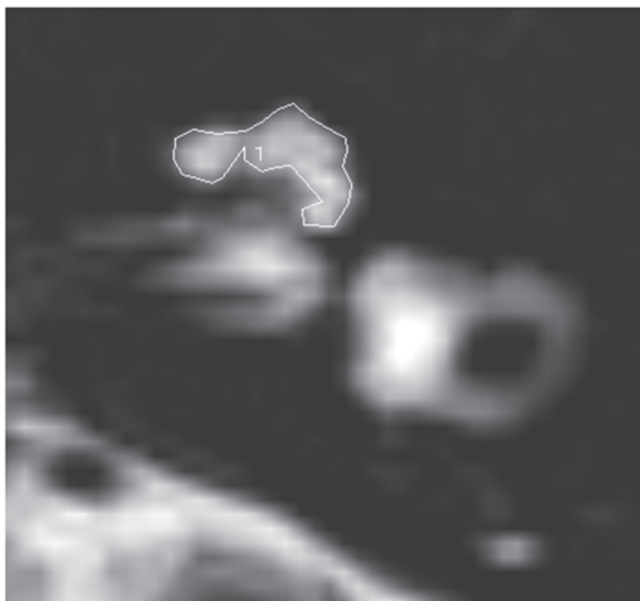

Fig. 1. An example of the region of interest setting around the cochlear fluid on a mid-modiolar section of magnetic resonance cisternography. This image was obtained using SPACE sequence in a volunteer.

Statistical Analysis

Differences in the CNR from FL (CNR-FL) and HF (CNR-HF) among the volunteer, mild hearing loss, and severe hearing loss groups were tested by one-way analysis of variance (ANOVA) and Scheffé post hoc analysis or, when the null hypothesis of equal variance is rejected, by Tamhane's post hoc analysis. Further, we performed receiver operating characteristic (ROC) analysis to evaluate discrimination performance of CNR-FL and CNR-HF in the detection of sudden deafness, and used the area under the ROC curve as an index of detection performance. For the mild and severe hearing loss groups, we also analyzed the linear relationship between CNR-FL or CNR-HF and "hearing disability ratio" by Pearson's correlation coefficient. In this study, "hearing disability ratio" means the ratio of absolute difference in hearing level between the affected and unaffected sides to the hearing level of the unaffected side; a linear regression line was calculated by the York method. Furthermore, for the mild and severe hearing loss groups, univariate logistic regression analyses were performed in order to identify a relationship between CNR-FL or CNR-HF and recovery of hearing ability. We analyzed the linear relationship between the days from onset to MR examination and CNR-FL or CNR-HF by Pearson's correlation coefficient.

We used SPSS 22 software (SPSS Inc., Chicago, Illinois, USA) for all statistical analyses, and adopted 5% as the level of significance for the statistical tests.

Results

The CNR values of the subjects are listed in Table 1. Mean CNR values ± SD on FL and HF were 0.3 ± 0.3, 0.1 ± 0.3 for the volunteer group, 0.0 ± 0.6, 1.7 ± 0.8 for the mild hearing loss group and 1.2 ± 1.8, 3.3 ± 1.5 for the severe hearing loss group, respectively (Figs. 2–4).

Fig. 5 shows the distribution of CNR-HF for the volunteer, mild hearing loss, and severe hearing loss groups. There was a statistically significant difference in the mean CNR-HF among the three groups ($P < 0.001$). Furthermore, based on pairwise comparisons, there was a statistically significant difference between each group in mean CNR-HF ($P < 0.05$).

Fig. 6 shows the distribution of CNR-FL for the volunteer, mild hearing loss, and severe hearing loss groups. There was no statistically significant difference in mean CNR-FL between the three groups ($P = 0.074$).

As for the detection performance of sudden deafness, the area under the ROC curve for CNR-FL was estimated to be 0.518 (95% confidence interval: 0.329–0.706), whereas the area under the ROC curve for CNR-HF was 1.

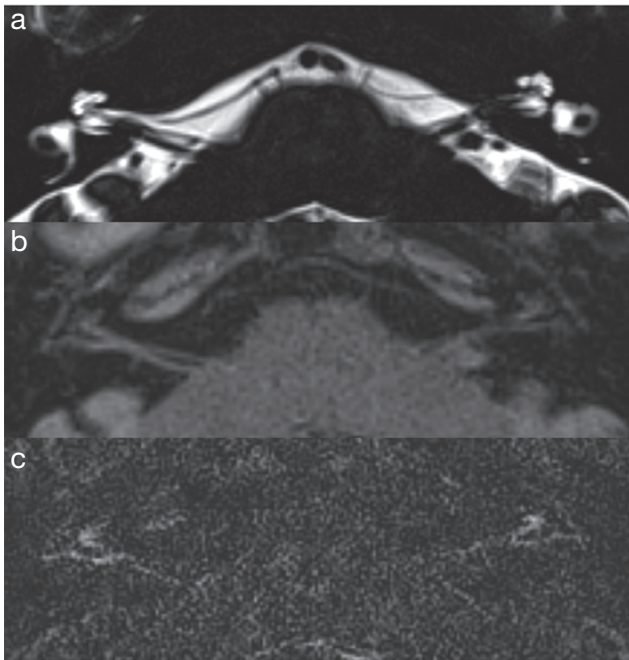Fig. 7 shows the relationship between CNR-HF and "hearing disability ratio" for the mild and severe hearing

Fig. 2. A 53-year-old male volunteer. Magnetic resonance cisternography (**a**), regular contrast three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) (FL, **b**) and heavily T_2-weighted 3D-FLAIR (HF, **c**). The contrast-to-noise ratio between the right and left cochlea is –0.1 on FL and 0.2 on HF. There is no signal increase in the cochlear fluid on either FL or HL.
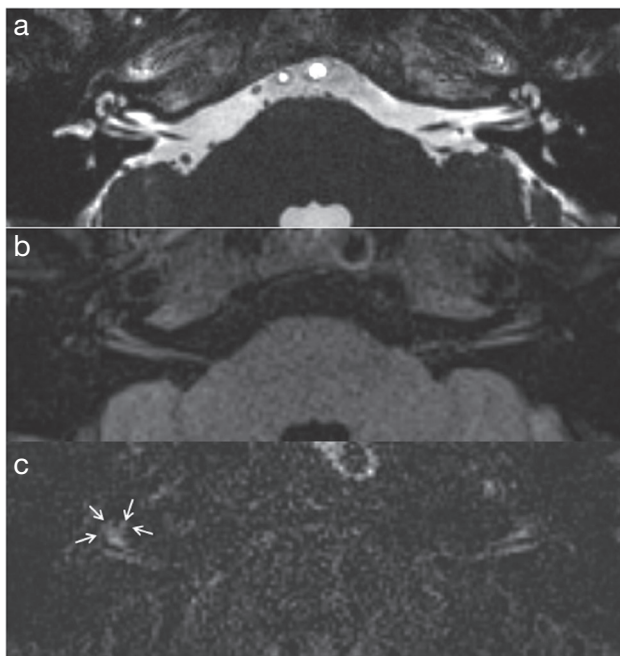

Fig. 3. A 33-year-old man with mild sudden sensorineural hearing loss (SNHL) in his right ear. Magnetic resonance cisternography (**a**), regular contrast three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) (FL, **b**) and heavily T_2-weighted 3D-FLAIR (HF, **c**). The contrast-to-noise ratio between the affected and non-affected cochlea is 0.3 on FL and 2.9 on HF. There is a clear signal increase in the right cochlear fluid on HF (arrows, c), but unclear on FL (b).
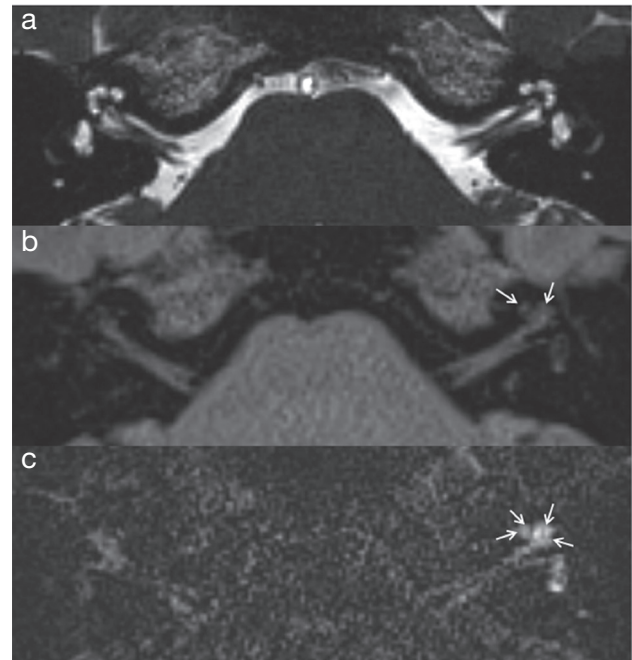

Fig. 4. A 35-year-old woman with severe sudden sensorineural hearing loss (SNHL) in her left ear. MR cisternography (**a**), regular contrast three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) (FL, **b**) and heavily T_2-weighted 3D-FLAIR (HF, **c**). The contrast-to-noise ratio between the affected and non-affected cochlea is 3.3 on FL and 5.8 on HF. There is a clear signal increase in the left cochlear fluid on FL (arrows, b) and HF (arrows, c), although the signal increase is visually more prominent on HF (c) than on FL (b).

loss groups. A moderate linear correlation was observed between them; Pearson's correlation coefficient (r) was 0.427 ($P = 0.033$) and the estimated slope coefficient and intercept ($\pm$ standard error) of the linear regression line was 0.491 ± 0.147 and 1.150 ± 0.552, respectively. Fig. 8 shows the relationship between CNR-FL and "hearing disability ratio" for the mild and severe hearing loss groups. There was no linear correlation between them; Pearson's correlation coefficient (r) was 0.280 ($P = 0.175$) and the estimated slope coefficient and intercept ($\pm$ standard error) of the linear regression line was 0.425 ± 0.166 and -0.585 ± 0.622, respectively.

Both CNR-HF and CNR-FL showed no relationship to the recovery of hearing ability by univariate logistic regression analysis.

No significant linear relationship between the days from onset to MR examination and CNR-FL or CNR-HF was observed; Pearson's correlation coefficient (r) was 0.108 ($P = 0.607$) for CNR-FL and 0.150 ($P = 0.474$) for CNR-HF.

Discussion

Previous studies have utilized subjective evaluation for the recognition of high signal intensity in the
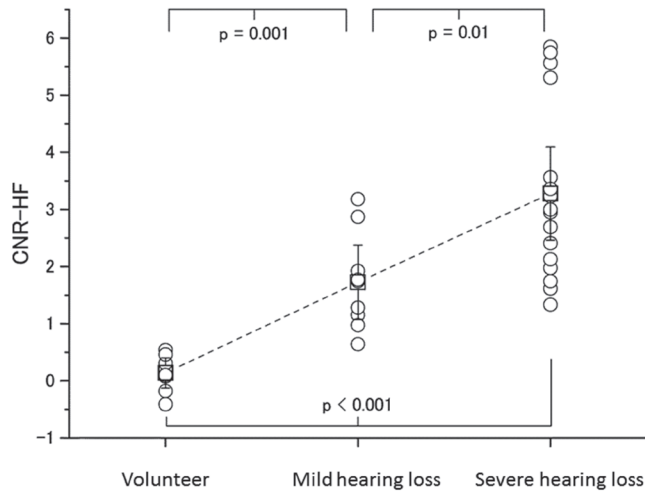
Fig. 5. Distribution of CNR-HF in the volunteer, mild hearing loss, and severe hearing loss groups. There was a statistically significant difference in the mean CNR-HF among the three groups (*P* < 0.001). Open circles show the distribution of CNR-HF in the volunteer, mild hearing loss, and severe hearing loss groups. Open squares show the mean and error bars indicate the 95% confidence intervals. CNR, contrast-to-noise ratio; HF: heavily T$_2$-weighted three-dimensional fluid-attenuated inversion recovery.
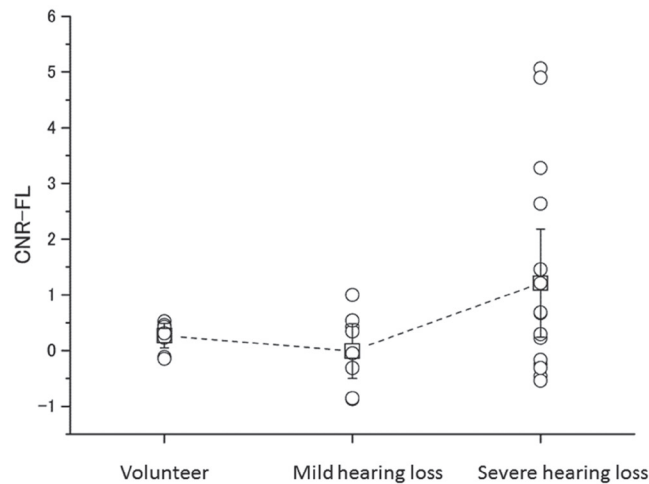

Fig. 7. Scattergram showing the relationship between "hearing disability ratio" and CNR-HF. A moderate linear correlation was observed between them; Pearson's correlation coefficient (*r*) is 0.427 (*P* = 0.033). CNR, contrast-to-noise ratio; HF: heavily T$_2$-weighted three-dimensional fluid-attenuated inversion recovery.

Fig. 6. Distribution of CNR-FL in the volunteer, mild hearing loss, and severe hearing loss groups. There was no statistically significant difference in the mean CNR-FL among the three groups (*P* = 0.074). Open circles show the distribution of CNR-FL in the volunteer, mild hearing loss, and severe hearing loss groups. Open squares show the mean and error bars indicate the 95% confidence intervals. CNR, contrast-to-noise ratio; FL, regular contrast three-dimensional fluid-attenuated inversion recovery.

Fig. 8. Scattergram showing the relationship between "hearing disability ratio" and CNR-FL. There was no linear correlation between them; Pearson's correlation coefficient (*r*) is 0.280 (*P* = 0.175). CNR, contrast-to-noise ratio; FL, regular contrast three-dimensional fluid-attenuated inversion recovery.

cochlea by FL.[1,4,5,7,9] In the present study, we conducted quantitative analysis to rule out observer bias. HF is more sensitive than FL for the detection of high signals in the cochlea. Furthermore, in the detection of sudden S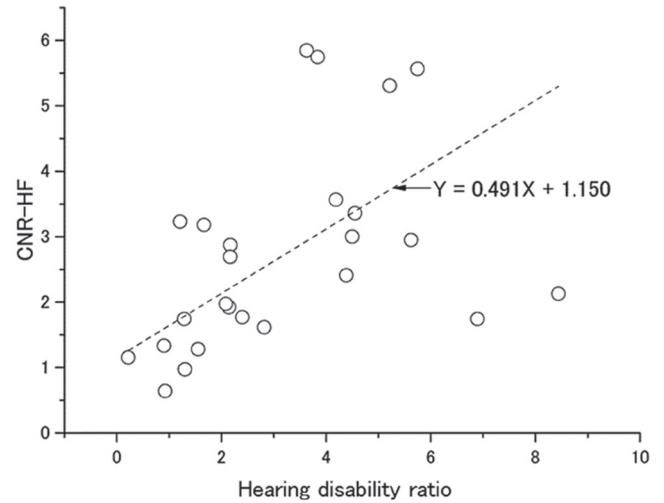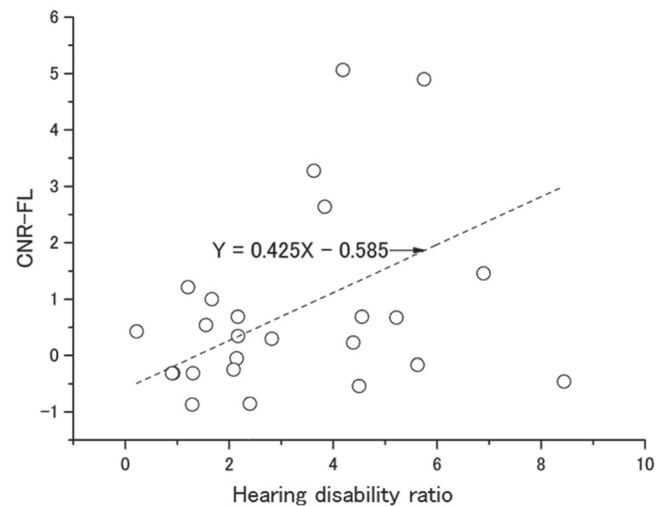NHL, the area under the ROC curve for CNR-FL was estimated to be 0.518, whereas the area under the ROC curve for CNR-HF was 1. HF thus has an advantage over FL in the evaluation of sudden SNHL.

However, both CNR-HF and CNR-FL showed no correlation with recovery of hearing level. This might be due to the long time interval (more than 30 days on average) between the onset of hearing loss and MR examination in the cohort of this study. Further study which includes more acute phase patients might be necessary to clarify the prognostic values of HF for sudden SNHL.

The signal increase of the labyrinthine fluid on FL in sudden SNHL has been speculated to represent higher protein concentrations such as inflammatory exudates or minor hemorrhage.[1,3,7] It can be reasonably speculated that the high signal of the labyrinthine fluid in sudden SNHL would gradually diminish over time. However, this time course of signal alteration has not been investigated in patients with sudden SNHL.

In the present study, we compared the CNR between affected and non-affected ears for the evaluation of unilateral sudden SNHL. Thus, this method might not be effective for patients with bilateral sudden SNHL. However, bilateral sudden SHNL is rare and a different disease entity from the unilateral condition. The bilateral condition is mostly associated with serious systemic conditions, such as toxic, neoplastic, vascular, autoimmune, infectious, or iatrogenic etiologies among others.[25] The bilateral condition has a higher prevalence of morbidity and mortality. In other words, bilateral disease is a medical emergency as it is closely associated with serious systemic disease and poorer hearing prognoses.[25] Thus, in patients with bilateral sudden SNHL, inner ear MR imaging might not be a high priority.

Our study has some limitations that should be noted. We applied the generalized autocalibrating partially parallel acquisitions (GRAPPA) parallel imaging technique and measured noise level in the air space, but use of this parallel imaging technique and a multi-channel phased array coil is reported to result in uneven noise distribution across the image.[26] However, we measured the CNR of cochlear lymph fluid in each subject. The signal in the cochlea and noise in the air space in the lower corner of the image were estimated at identical regions in each subject for both FL and HF, and those regions differed little among subjects. The consistent geometrical position of the noise measurement reduces the systemic error of CNR calculations when comparing CNR values between two protocols. Furthermore, error induced by parallel imaging reconstruction would be quite small when the g-factor of a 32-channel array coil for an acceleration factor of 2 in the GRAPPA technique is almost 1.[10,27] Therefore, although our method of measuring CNR is not ideal, we believe it is reasonable for the purposes of our study.[28]

We employed two MR cisternography techniques: constructive interference in steady-state (CISS) for patients and SPACE for volunteers. While the shape of the vestibule is sometimes distorted on CISS, the shape of the cochlea is much less distorted on CISS even with some banding artifacts in the cochlear turns.[29] Therefore, differences in the MR cisternography technique had little effect on the results of the present study.

Further study would be warranted to establish the value of HF in the stratification of patients with sudden SNHL, prediction of hearing prognosis, and treatment monitoring.

Conclusion

HF is more sensitive to high signals in the cochlea of ears with sudden SNHL than FL. The signal increase in the cochlea can be detected by HF even for mild hearing loss.

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