Original Article

The value of postcontrast delayed 3D fluid-attenuated inversion recovery MRI in the diagnosis of unilateral peripheral vestibular dysfunction

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Background: Clinically, unilateral peripheral vestibular dysfunction (UPVD) with dizziness or vertigo as the chief complaint is quite common. This study aimed to investigate the correlations between 3-dimensional fluid-attenuated inversion recovery magnetic resonance imaging (3D-FLAIR MRI) findings and cochleovestibular function test results in patients with UPVD and to explore the possible etiologies of UPVD.

Methods: This retrospective study enrolled 76 patients with UPVD. Endolymphatic hydrops (EH) and perilymphatic enhancement (PE) in the vestibule and cochlea on 3D-FLAIR images, their correlations with the parameters of the cochleovestibular function test and vascular risk factors, and the immunological findings of patients with EH and PE were assessed.

Results: Of the included patients, 48.7% showed positive MRI findings (the presence of EH and PE on 1 side). The pure-tone average (PTA) was higher in patients with cochlear PE than in those with vestibular (P=0.014) and cochlear EH (P=0.02). The canal paresis (CP) value was also higher in patients with vestibular PE than in those with vestibular (P=0.002) and cochlear EH (P=0.003). Video head impulse test (vHIT) gains were lower in patients with vestibular and cochlear PE than in those with vestibular and cochlear EH (P<0.001). A positive correlation was observed between the degree of vestibular and cochlear EH and PTA (both P values <0.001). PTA and CP with a cutoff value of 32 dB and 46.5%, respectively, yielded high sensitivity and specificity in determining positive MRI findings (P<0.001 and P=0.029, respectively). The prevalence of vascular risk factors was significantly higher in patients with PE than in those with EH (P=0.033).

Conclusions: (I) Nearly half of the patients UPVD exhibited abnormal MRI findings. Cutoff values for PTA and CP of 32 dB and 46.5%, respectively, indicated that patients were more likely to have abnormal imaging findings. (II) The severity of EH was positively correlated with hearing impairment. (III) Patients with PE showed severe hearing impairment and vestibular dysfunction, which was presumed to be associated

with vascular damage.

Keywords: Unilateral peripheral vestibular dysfunction (UPVD); cochleovestibular function tests; postcontrast delayed 3-dimensional fluid-attenuated inversion recovery magnetic resonance imaging (postcontrast delayed 3D-FLAIR MRI); endolymphatic hydrops; perilymphatic enhancement

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Introduction

Clinically, unilateral damage to the peripheral vestibular pathway, which includes vestibular hair cells and vestibular nerves, caused by any physicochemical factors can result in asymmetric damage to the bilateral vestibular system, leading to the occurrence of corresponding symptoms of imbalance, such as dizziness or vertigo, spontaneous nystagmus (SN), and severe nausea and vomiting. This condition is known as unilateral peripheral vestibular dysfunction (UPVD). A German multicenter study of 34,860 patients with dizziness or vertigo reported that about 9.1% of patients developed UPVD, indicating a high prevalence among patients with dizziness or vertigo (1). Presently, the etiologies of UPVD remain unclear. Previous study suggests that the occurrence of UPVD may be related to viral infection, while other etiologies such as vascular risk factors and autoimmune reactions have also been proposed (2). In clinical practice, the diagnosis of UPVD relies mainly on patients' medical history and the techniques used for vestibular function evaluation, including the caloric test, video head impulse test (vHIT), and vestibular-evoked myogenic potentials; physicians can also apply these tests to evaluate the function of 3 semicircular canals at different frequencies as well as the function of the utricle and saccule (3,4). In recent years, the development of noninvasive magnetic resonance imaging (MRI) technology with diverse models, sequences, and high spatiotemporal resolution (5) has provided new ideas for the diagnosis of UPVD. Currently, nonvestibular assessment techniques, such as MRI of the labyrinth, can provide assistance in etiological diagnosis and precise localization diagnosis of side involvement in patients with UPVD, an have been widely used in clinical practice.

In 2006, Naganawa *et al.* (6) first performed 3-dimensional fluid-attenuated inversion recovery (3D-FLAIR) MRI of the labyrinth after intravenous administration of gadolinium (Gd) in healthy participants. It is commonly accepted that the biological barriers of the membranous labyrinth of the inner ear, such as the blood-perilymph and blood–endolymph barriers have the property of selective transport of different substances, which allow the Gd contrast agent to selectively enter into the perilymphatic space, thus leading to the enhancement of the perilymph (high signal intensity on MRI), whereas the endolymphatic space shows a low signal intensity on MRI. Based on the differences in signals of perilymphatic and endolymphatic spaces in the labyrinth detected, postcontrast delayed 3D-FLAIR MRI can not only help to visualize the fine structures of the labyrinth but also provide clinicians with diagnostic evidence of endolymphatic hydrops (EH), blood-labyrinth barrier (BLB) disruption, and vestibular nerve abnormalities.

In previous studies, many scholars have applied the combination of cochleovestibular function tests and postcontrast delayed 3D-FLAIR MRI to investigate the relationship between imaging findings of the labyrinth and cochleovestibular function test results; however, the results of these studies are inconsistent. Studies of patients with Menière disease (MD) have revealed a positive correlation between audiological test results and EH severity (7-9). Results regarding the correlations between vestibular function test results and the extent of EH have varied among studies. Kahn *et al.* (9) reported there to be no correlation between EH severity and vestibular function test results. Sluydts *et al.* (10) indicated that only the highest grades of cochlear and vestibular EH were associated with vestibular hypofunction. A study of patients with sudden sensorineural hearing loss (SSHL) showed that the extent of high signal in the cochlea on the affected side was correlated with the degree of vestibular dysfunction and hearing loss (11,12).

Although UPVD is quite common in clinical practice, its etiology is still unclear, and the relationship between cochleovestibular test results and cochleovestibular dysfunction is still controversial, thus warranting further in-depth investigation. In 2019, Bernaerts *et al.* (13) proposed a new classification method for labyrinth imaging, which evaluates both signs of perilymphatic enhancement (PE) and

EH grading on MRI, reporting the high accuracy for the diagnosis of MD, with a sensitivity of 85% and a specificity of 92%. In the present study, we performed postcontrast delayed 3D-FLAIR MRI in patients with UPVD, evaluated the grades of EH in these patients according to the abovementioned method, and subsequently analyzed their correlations with cochleovestibular test results. We also observed the vascular risk factors and immunological findings in patients with PE and EH to explore the possible etiologies and pathogenesis of UPVD.

Methods

Patients

A total of 76 patients with UPVD who had a unilateral canal paresis (CP) value of caloric test greater than 25%, dizziness or vertigo as the chief complaint, and who attended the neurology department of our hospital from May 2020 to June 2022 were included. Out of these 76 patients, 39 were diagnosed with right-sided UPVD, and the remaining 37 patients were diagnosed with left-sided UPVD. There were 29 males and 47 females with a male to female ratio of 1:1.6 and a mean age of 51.82±13.16 years (range, 20–81 years). The clinical baseline data of the patients were collected systematically, including the course of disease, the duration of vertigo attack, SN without fixation, ear fullness, and tinnitus. The time interval between cochleovestibular function tests and MRI examination was also recorded.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of Aerospace Center Hospital (Peking University Aerospace School of Clinical Medicine; No. 2021-ASCH-010). Informed consent was obtained from all the patients.

MRI protocol

MRI scans of the entire temporal bone were performed using a 3.0 T MRI scanner (MAGNETOM Avanto, Siemens Healthineers, Erlangen, Germany) with an 8-channel head coil. The MRI protocol was as follows: plain T1-weighted imaging (T1WI), fast-spin-echo (FSE) T2-weighted imaging (T2WI), and T2-driven equilibrium high resolution (DRIVE-HR) in the transverse plane; enhanced T1WI in the transverse and coronal planes; and 4-hour-delayed Gd-enhanced 3D FLAIR. Gadopentetate dimeglumine (Gd-DTPA; Magnevist, Bayer Healthcare, Leverkusen, Germany) was used. A double dose of Gd-DTPA (0.2 mmol/kg of body weight) was routinely injected at a rate of 2.0 mL/s via the antecubital vein using a high-pressure syringe (Ulrich Medical, Ulm, Germany), which was followed by an intravenous push of 20 mL of saline. The following acquisition parameters were used: T1WI—repetition time (TR) 687 ms, echo time (TE) 10 ms, echo train length (ETL) 8, matrix size 256×256, number of excitations 2.5, thickness 2.0 mm, slices 16, field of view (FOV), 18 cm × 18 cm, and time of acquisition 2 min 4 s; FSE T2WI—TR 3,000 ms, TE 90 ms, ETL 16, matrix size 300×232, number of excitations 2, thickness 2.0 mm, slices 16, FOV 18 cm × 18 cm, and time of acquisition 2 min 18 s; T2-DRIVE-HR—TR 1,500 ms, TE 214 ms, ETL 54, matrix size 300×300, number of excitations 1, thickness 0.8 mm, slices 64, FOV 18 cm × 18 cm, and time of acquisition 3 min 3 s; and 3D-FLAIR—TR 9,000 ms, TE 446 ms, inversion time 1,800 ms, ETL 140, matrix size 264×256, number of excitations 5, thickness 1.2 mm, slices 24, FOV 18 cm × 18 cm, and time of acquisition 9 min 2 s.

Imaging analysis

We used a Philips IntelliSpace MRI postprocessor (Philips Healthcare, Best, The Netherlands). One physician standardized the images and transferred the images to the picture archiving and communication system (PACS). The image was then evaluated by an experienced radiologist and a neurologist.

The degree of cochlear and vestibular EH was graded according to the relative area of Gd contrast medium-enhanced perilymph and indirectly displayed nonenhanced endolymph in the axial plane. According to the criteria previously described by Bernaerts *et al.* (13), the degree of vestibular EH was classified as none, grade I, and grade II (vestibular EH grade III was not found in the patients with UPVD included in this study), while the degree of cochlear EH was classified as none, grade I, and grade II (*Figure 1*). In patients with a normal vestibule without EH, the saccule was smaller than the utricle and was less than half of the vestibular area; in patients with vestibular EH grade I, the saccule was equal to or larger than the utricle; in patients with vestibular EH grade II, there was a confluence of the saccule and utricle, but peripheral lymphatic rim enhancement was still visualized. In patients with normal cochlea without EH, the scala tympani and scala vestibuli were visualized; in patients with cochlear EH grade I, the scala media was indirectly visualized as a black space; in patients with cochlear EH grade II, the scala media

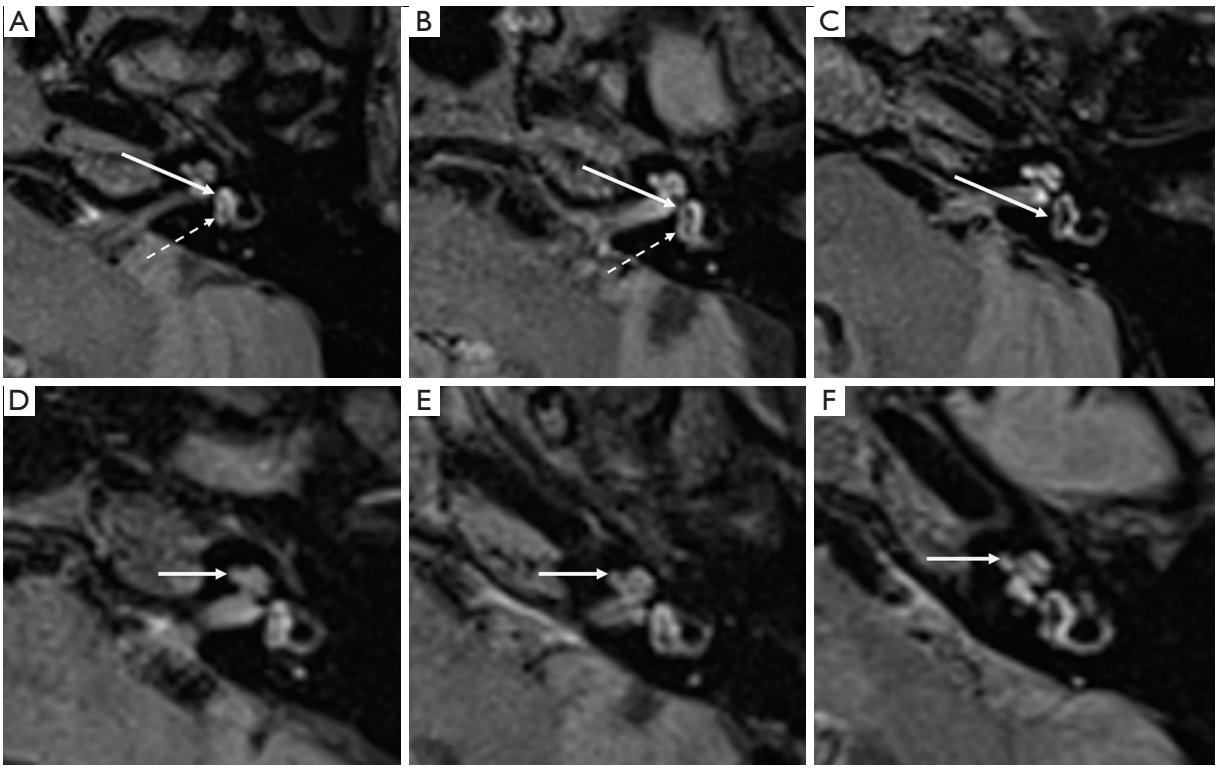

Figure 1 Grades of vestibular and cochlear EH. (A) Vestibular EH grade 0 (normal vestibule). The saccule (white solid arrow) and utricle (white dashed arrow) appear separate, and the area of the saccule is less than half of the vestibular area. (B) Vestibular EH grade I. The saccule (white solid arrow), which is usually smaller than the saccule (white dashed arrow), has become equal to or larger than the utricle, but their confluence has not yet occurred. (C) Vestibular EH grade II. There is a confluence of the saccule and utricle (white solid arrow), but peripheral lymphatic rim enhancement is still visible. (D) Cochlear EH grade 0 (normal cochlea). The scala tympani and scala vestibuli are visible (the white solid arrow indicates the cochlea). (E) Cochlear EH grade I. The scala media is indirectly visible as a black space (the white solid arrow indicates the cochlea). (F) Cochlear EH grade II. The scala media is enlarged, and the scala vestibuli is completely obliterated (the white solid arrow indicates the cochlea). EH, endolymphatic hydrops.

was enlarged, and the scala vestibuli had been obliterated completely.

With regard to the evaluation of PE, based on the asymmetry of bilateral ears, we visually compared the enhancement of the vestibular and cochlear perilymph between the ipsilateral vestibular dysfunction side (affected side) and the normal side. If asymmetrical enhancement was found in 1 side of the labyrinth, PE was considered to be present. The bilateral ears of all patients were evaluated and divided into vestibular PE and cochlear PE according to the imaging site (*Figures 2-4*).

Video head impulse test

vHIT was performed using EyeSeeCam (Interacoustics, Middelfart, Denmark). Patients were in the sitting position and wore an eye mask. They were instructed to fix their eyes on a target at eye level and at a distance of 1.5 m. The examiner stood behind the patient while holding the patient's head between both hands. Subsequently, 20 head impulses were delivered in each canal plane in a brief, rapid, passive manner, with the angular velocity being 150°–250°/s for the horizontal canal impulses. The vHIT software was used to record the average slow phase vestibulo-ocular reflex (VOR) gain values (the ratio of eye velocity to head velocity at 60 s), with an VOR gain of the horizontal canal <0.8 indicating abnormal vHIT (14).

Caloric test

The caloric test was performed using the videonystagmography (Interacoustics). Patients were positioned in the supine

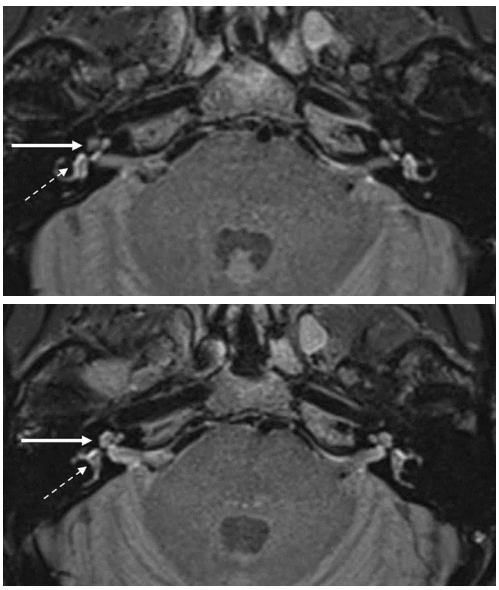

Figure 2 Postcontrast delayed 3D-FLAIR MRI revealing normal signal intensity in the perilymph of the bilaterally vestibule and cochlea. The white solid arrows indicate the cochlea, and the white dashed arrows indicate the vestibule. 3D-FLAIR MRI, 3-dimensional fluid-attenuated inversion recovery magnetic resonance imaging.

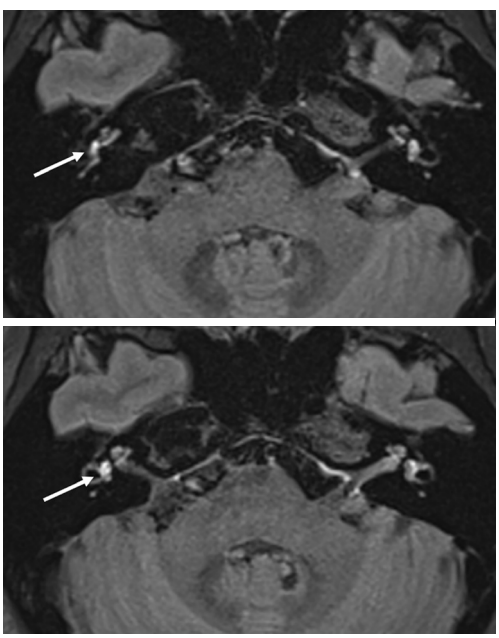

Figure 3 Postcontrast delayed 3D-FLAIR MRI revealing high signal intensity in the perilymph of the right vestibule. The solid white arrows indicate the vestibule. 3D-FLAIR MRI, 3-dimensional fluid-attenuated inversion recovery magnetic resonance imaging.

position in a semi-dark room, with their head tilted up about 30° and with goggles placed over their eyes. The right and left external auditory canals were irrigated with hot air at 50 ℃ and cold air at 24 ℃, respectively, for 1 min. Nystagmus evoked was recorded using videonystagmography in the dark, with the patients' eyes open. The CP value was calculated using Jongkees formula (15). CP ≥25% was defined as unilateral horizontal semicircular canal dysfunction (16).

Observation of vascular risk factors and immunological indicators

The vascular risk factors of all patients, including hypertension, diabetes, and hyperlipidemia were collected. All patients received immunological tests, including measurement of anti-thyroglobulin antibodies (Tg-Ab), anti-thyroperoxidase antibodies (TPO-Ab), rheumatoid factor, antinuclear antibodies, and antiphospholipid antibodies in serum.

Statistical analysis

Continuous variables are expressed as mean and standard deviation (SD). Independent sample *t*-test was used to compare the mean between the two groups of normal distribution, and one-way analysis of variance (ANOVA) was used to compare the mean between multiple groups. Mann-Whitney test was used to compare the mean of non-normal distribution between the two groups, and Kruskal-Wallis test was used to compare the results between multiple groups. Categorical variables are reported as percentages and were compared using the chi-squared test with Yates continuity correction or Fisher exact test, as appropriate. Spearman correlation analysis was performed to analyze the correlations between the degree of EH and cochleovestibular function test results. All reported P values are two-tailed, and $P<0.05$ was considered statistically significant. All statistical analyses were performed with SPSS 25.0 (IBM Corp., Armonk, NY, USA).

Results

Postcontrast delayed 3D-FLAIR MRI findings

Among the 76 patients with UPVD included in the study, there were 37 patients with MRI-positive (MRI+) findings (MRI+ group: the presence of vestibular EH, cochlear EH, vestibular PE, and cochlear PE on 1 side) and 39 patients with MRI-negative (MRI–) findings (MRI– group). The rate of positive findings on 3D-FLAIR MRI was 48.7%

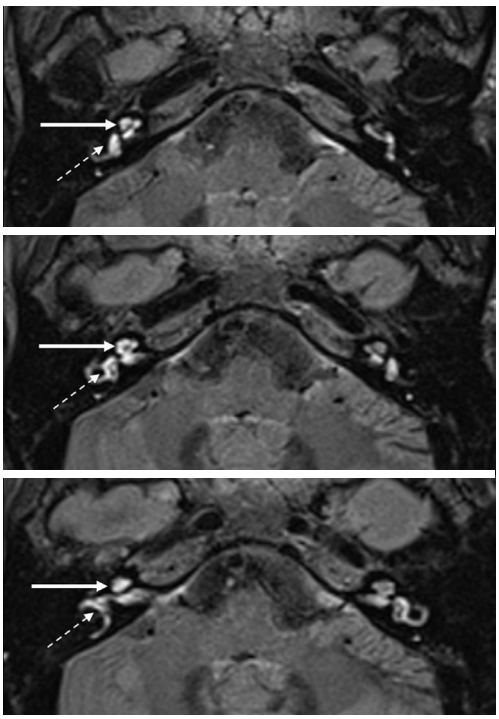

Figure 4 Postcontrast delayed 3D-FLAIR MRI revealed high signal intensity in the perilymph of the right vestibule and cochlea. The white solid arrows indicate the cochlea, and the white dashed arrows indicate the vestibule. 3D-FLAIR MRI, 3-dimensional fluid-attenuated inversion recovery magnetic resonance imaging.

Table 1 The presence of different grades of vestibular EH, cochlear EH, vestibular PE, and cochlear PE in patients with UPVD

Variables	Vestibular	Cochlear
EH		
Grade 0	53.9% (41/76)	69.7% (53/76)
Grade I	22.4% (17/76)	15.8% (12/76)
Grade II	11.8% (9/76)	7.9% (6/76)
PE	11.8% (9/76)	6.6% (5/76)

Categorical variables are reported as percentages (numbers). EH, endolymphatic hydrops; PE, perilymphatic enhancement; UPVD, unilateral peripheral vestibular dysfunction.

in patients with UPVD. Vestibular EH grade 0 was noted in 53.9% (41/76) of the patients, vestibular EH grade I in 22.4% (17/76) of the patients, and vestibular EH grade II in 11.8% (9/76) of the patients. Cochlear EH grade 0 was noted in 69.7% (53/76) of the patients, cochlear EH grade I in 15.8% (12/76) of the patients, and cochlear EH grade II in 7.9% (6/76) of the patients. The presence of vestibular and cochlear PE was found in 11.8% (9/76) and 6.6% (5/76) of the patients, respectively (*Table 1*).

Clinical baseline data of patients with EH and PE

The average age of patients in the EH group was significantly older than that in the PE group (58.39±10.61 *vs.* 48.33±13.59; P=0.027). The average course of disease in the EH group was longer than that in the PE group (35.54±48.60 *vs.* 6.78±9.76; P=0.026). In terms of concomitant symptoms, the incidence of SN without fixation in the PE group was higher than that in the EH group (39.3% *vs.* 88.9%; P=0.012; *Table 2*).

Results from pure tone audiometry

The mean pure-tone average (PTA) was 36.49±28.97 dB. The PTA was significantly lower in the MRI– group than in the MRI+ group (19.15±15.86 *vs.* 54.76±28.55; P<0.001). A PTA cutoff of 32 dB had high sensitivity and specificity in determining whether the patients had MRI+ findings [area under the curve (AUC) =0.832; P<0.001; *Figure 5*].

In the MRI+ group, there were statistically significant differences in PTA between patients with vestibular EH, cochlear EH, vestibular PE, and cochlear PE (P=0.019). PTA was significantly higher in patients with cochlear PE than in those with vestibular EH (95.80±9.39 *vs.* 54.92±21.95; P=0.014) and cochlear EH (95.80±9.39 *vs.* 55.33±18.69; P=0.02; *Figure 6*).

Further analysis of patients with vestibular EH showed that there were statistically significant differences in PTA between patients with vestibular EH grades 0, I, and II (P<0.001). PTA was significantly lower in patients with vestibular EH grade 0 than in those with vestibular EH grade I (20.14±16.11 *vs.* 53.18±26.65; P<0.001) and vestibular EH grade II (20.14±16.11 *vs.* 58.22±8.12; P<0.001; *Table 3*; *Figure 6*). The degree of vestibular EH was positively correlated with PTA (r=0.707; P<0.001; *Figure 7*).

Further analysis of patients with cochlear EH showed that there were statistically significant differences in PTA between patients with cochlear EH grades 0, I, and II (P<0.001). PTA was significantly lower in patients with cochlear EH grade 0 than in those with cochlear EH grade I (24.49±21.95 *vs.* 50.92±17.69; P<0.001) and cochlear EH grade II (24.49±21.95 *vs.* 64.17±18.73; P=0.002; *Table 3*; *Figure 6*). There was a positive correlation between the degree of cochlear EH and PTA (r=0.577; P<0.001; *Figure 7*).

Table 2 Comparison of clinical characteristics between patients with EH and PE

Characteristics	EH	PE	P value
Age (years)	58.39±10.61	48.33±13.59	0.027*
Sex (female/male)	11/17	5/4	0.391
Course of disease (days)	35.54±48.60	6.78±9.76	0.026*
Duration of vertigo			0.104
<1 hour	10 (35.7)	0	
≥1 hour–1 day	13 (46.4)	7 (77.8)	
>1 day	5 (17.9)	2 (22.2)	
Associated symptoms			
Tinnitus	21 (75.0)	6 (75.0)	0.624
Ear fullness	12 (42.9)	1 (11.1)	0.083
SN without fixation	11 (39.3)	8 (88.9)	0.012*
Time interval between cochleovestibular function tests and MRI (days)	15.61±43.24#	4.22±2.95	0.240

Categorical variables are reported as numbers (percentages), and continuous variables are presented as mean ± standard deviation. *, P<0.05; #, the median time from cochleovestibular function tests to MRI in patients with EH was 5 days, with a maximum of 220 days and a minimum of 1 day. EH, endolymphatic hydrops; MRI, magnetic resonance imaging; PE, perilymphatic enhancement; SN, spontaneous nystagmus.

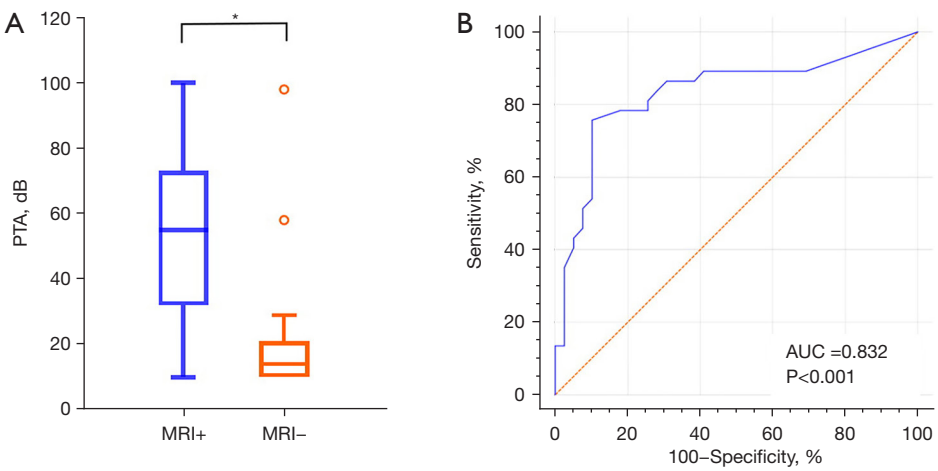

Figure 5 Comparison of PTA in patients with UPVD between the MRI+ and MRI– groups. (A) Comparison of the mean PTA in patients with UPVD between the MRI+ and MRI– groups. (B) Receiver operating characteristic curve of the PTA values for the determination of positive findings on 3D-FLAIR MRI in patients with UPVD. *, P<0.05. 3D-FLAIR, 3-dimensional fluid-attenuated inversion recovery; AUC, area under the receiver operating characteristic curve; MRI+, magnetic resonance imaging-positive; MRI–, magnetic resonance imaging-negative; PTA, pure-tone average; UPVD, unilateral peripheral vestibular dysfunction.

Caloric test results

The mean CP value of patients with UPVD was 56.54%±24.30%. The MRI– group showed significantly lower CP values than did the MRI+ group (51.10%±22.49% *vs.* 62.27%±25.12%; P=0.029). A CP cutoff value of 46.5% had high sensitivity and specificity in determining whether patients had MRI+ findings (AUC =0.643; P=0.029; *Figure 8*).

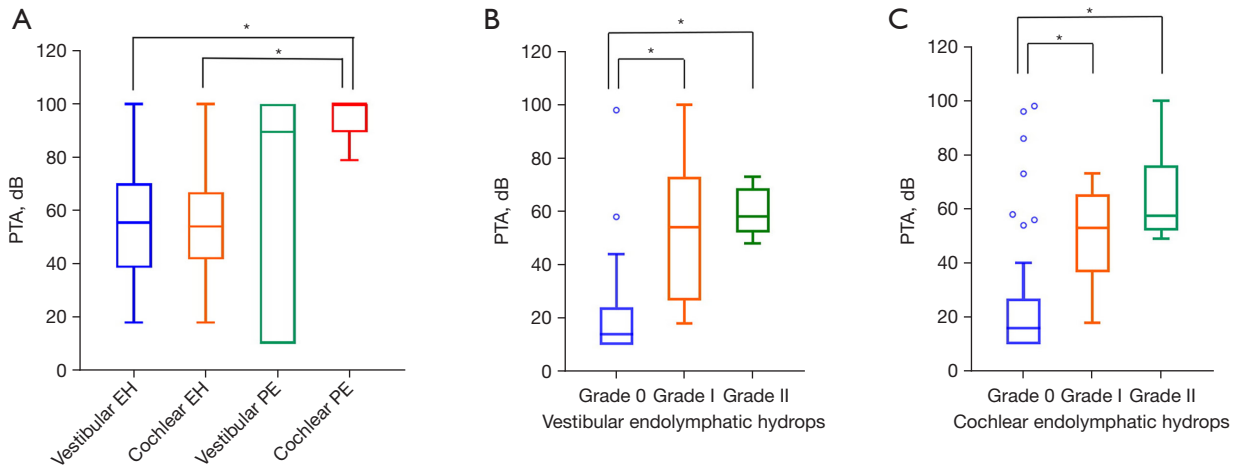

Figure 6 Comparison of PTA between UPVD patients with EH and PE. (A) Comparison of the mean PTA between UPVD patients with vestibular EH, cochlear EH, vestibular PE, and cochlear PE. (B) Comparison of the mean PTA between UPVD patients with different grades of vestibular EH. (C) Comparison of the mean PTA between UPVD patients with different grades of cochlear EH. *, P<0.05. EH, endolymphatic hydrops; PE, perilymphatic enhancement; PTA, pure-tone average; UPVD, unilateral peripheral vestibular dysfunction.

Table 3 Cochleovestibular function test results in UPVD patients with different grades of vestibular and cochlear EH

Variables	Grade 0	Grade I	Grade II	P value
Vestibular EH				
PTA (dB)	20.14±16.11	53.18±26.65	58.22±8.12	<0.001*
CP value (%)	51.22±22.77	58.24±22.93	51.56±8.13	0.374
vHIT gain	0.97±0.26	0.97±0.23	1.09±0.38	0.601
Cochlear EH				
PTA (dB)	24.49±21.95	50.92±17.69	64.17±18.73	<0.001*
CP value (%)	55.25±26.4	55.75±19.85	55.17±9.99	0.782
vHIT gain	0.93±0.28	1.02±0.23	1.06±0.91	0.606

Continuous variables are presented as the mean ± standard deviation. *, P<0.05. CP, canal paresis; EH, endolymphatic hydrops; PTA, pure-tone average; UPVD, unilateral peripheral vestibular dysfunction; vHIT, video head impulse test.

In the MRI+ group, statistically significant differences in CP value were found between patients with vestibular EH, cochlear EH, vestibular PE, and cochlear PE (P=0.008). Patients with vestibular PE showed significantly higher CP values than did those with vestibular EH (82.56%±29.79% *vs.* 55.69%±19.16%; P=0.002) and cochlear EH (82.56%±29.79% *vs.* 55.56%±16.86%; P=0.003; *Table 4*; *Figure 9*).

There were no statistically significant differences in CP value between patients with different grades of vestibular EH (P=0.374) or between patients with different grades of cochlear EH (P=0.782).

vHIT results

In this study, 64 out of the 76 patients underwent vHIT. In the MRI+ group, statistically significant differences in vHIT gains were observed between patients with vestibular EH, cochlear EH, vestibular PE, and cochlear PE (P<0.001). vHIT gains were significantly lower in patients with vestibular PE than in those with vestibular and cochlear EH (0.52±0.18 *vs.* 1.01±0.20, P=0.001; 0.52±0.18 *vs.* 1.03±0.19, P=0.001), and patients with cochlear PE showed significantly lower vHIT gains than did those with vestibular and cochlear EH (0.52±0.18 *vs.* 1.01±0.20, P=0.024; 0.52±0.18

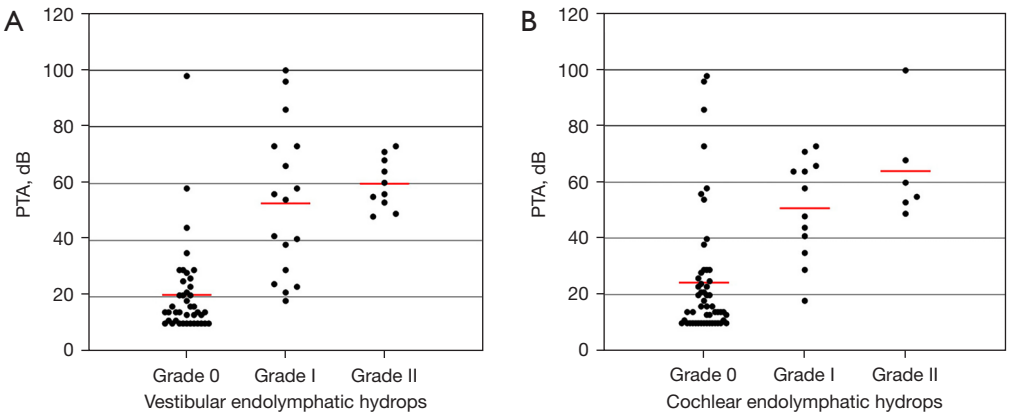

Figure 7 Correlation between different grades of EH and PTA. (A) Correlation between different grades of vestibular EH (x-axis) and PTA (y-axis) in patients with UPVD. A significant positive correlation was observed between the degree of vestibular EH and PTA (r=0.707; P<0.001). (B) Correlation between different grades of cochlear EH (x-axis) and PTA (y-axis) in patients with UPVD. A significant positive correlation was found between the degree of cochlear EH and PTA (r=0.577; P<0.001). Red lines indicate the mean PTA. EH, endolymphatic hydrops; PTA, pure-tone average; UPVD, unilateral peripheral vestibular dysfunction.

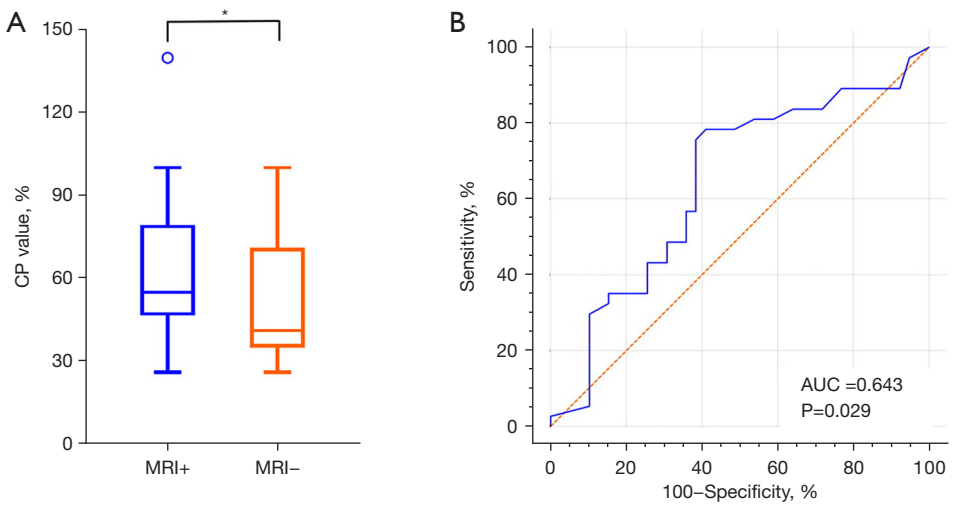

Figure 8 Comparison of the CP value in patients with UPVD between the MRI+ and MRI– groups. (A) Comparison of the mean CP value between the MRI+ and MRI– groups. (B) Receiver operating characteristic curve of CP values for the determination of positive findings on postcontrast delayed 3D-FLAIR MRI in patients with UPVD. *, P<0.05. 3D-FLAIR, 3-dimensional fluid-attenuated inversion recovery; AUC, area under the receiver operating characteristic curve; CP, canal paresis; MRI+, magnetic resonance imaging-positive; MRI–, magnetic resonance imaging-negative; UPVD, unilateral peripheral vestibular dysfunction.

vs. 1.03±0.19, P=0.021; *Table 4*; *Figure 9*).

There were no statistically significant differences in vHIT gains between the MRI+ and MRI– groups (P=0.117), between patients with different grades of vestibular EH (P=0.601), or between patients with different grades of cochlear EH (P=0.606).

Vascular risk factors and immunological indicators

Of the patients with EH (vestibular and cochlear), 42.9% (12/28) had vascular risk factors, while 88.9% (8/9) of those with PE (vestibular and cochlear) had vascular risk factors. The prevalence of vascular risk factors was significantly higher in patients with PE than in those with EH (P=0.033;

Table 4 Cochleovestibular function test results in UPVD patients with EH and PE along with the possible etiologies of UPVD

Classification	PTA (dB)	CP value (%)	vHIT gain	Vascular risk factors	Abnormal immunological indicators
EH				12 (42.9)	10 (35.7)
Vestibular EH	54.92±21.95	55.69±19.16	1.01±0.20		
Cochlear EH	55.33±18.69	55.56±16.86	1.03±0.19		
PE				8 (88.9)	1 (11.1)
Vestibular PE	57.67±45.71	82.56±29.79	0.52±0.18		
Cochlear PE	95.80±9.39	69.60±25.50	0.52±0.18		
P value	0.019*	0.008*	<0.001*	0.033*	0.687

Categorical variables are reported as numbers (percentages), and continuous variables are presented as the mean ± standard deviation. *, P<0.05. CP, canal paresis; EH, endolymphatic hydrops; PE, perilymphatic enhancement; PTA, pure-tone average; UPVD, unilateral peripheral vestibular dysfunction; vHIT, video head impulse test.

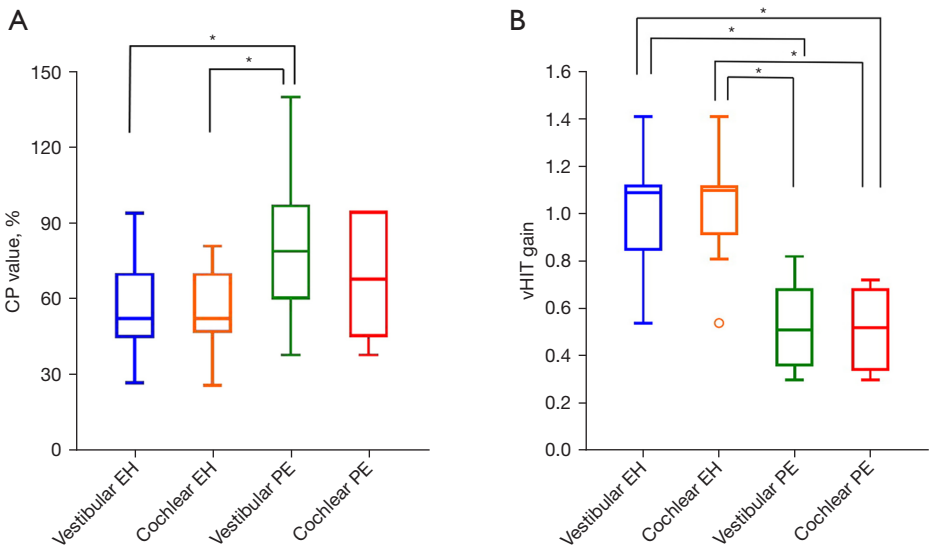

Figure 9 Comparison of the CP value and vHIT gains between UPVD patients with EH and PE. (A) Comparison of the mean CP value between UPVD patients with vestibular EH, cochlear EH, vestibular PE, and cochlear PE. (B) Comparison of the mean vHIT gains between UPVD patients with vestibular EH, cochlear EH, vestibular PE, and cochlear PE. *, P<0.05. CP, canal paresis; EH, endolymphatic hydrops; PE, perilymphatic enhancement; UPVD, unilateral peripheral vestibular dysfunction; vHIT, video head impulse test.

Figure 10).

Of the patients with EH, 35.7% (10/28) showed immune abnormalities, while this proportion was 11.1% (1/9) in those with PE. The prevalence of immune abnormalities was slightly higher in patients with EH than in those with PE, but the difference was not statistically significant (P=0.687; *Figure 10*).

Discussion

Cochleovestibular function tests in patients with UPVD in the MRI+ and MRI− groups

In recent years, the application of cochleovestibular function examinations such as the caloric test, vHIT, vestibular-evoked myogenic potentials, and auditory electrophysiology has not

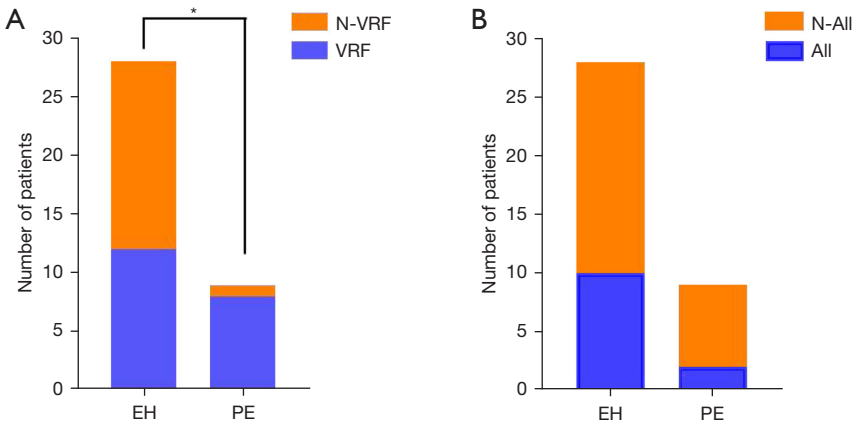

Figure 10 Comparison of vascular risk factors and immunological indicators between UPVD patients EH and PE. (A) Comparison of vascular risk factors between UPVD patients with EH and PE. (B) Comparison of immunological indicators between UPVD patients with EH and PE. *, P<0.05. AII, abnormal immunological indicators; EH, endolymphatic hydrops; N-AII, no abnormal immunological indicators; N-VRF, no vascular risk factors; PE, perilymphatic enhancement; UPVD, unilateral peripheral vestibular dysfunction; VRF, vascular risk factors.

only aided in the diagnosis of the location and the affected sides of UPVD but also facilitated differential diagnosis of peripheral and central vestibular disorders. Additionally, in clinical practice, the use of postcontrast delayed 3D-FLAIR MRI would facilitate further understanding of whether the specific lesion site in patients with UPVD is the vestibule or the cochlea and whether patients have BLB impairment or EH, as well as the possible etiologies. Therefore, in the present study, we performed both cochleovestibular function tests and postcontrast delayed 3D-FLAIR MRI in patients with UPVD, investigated the possible relationships between them, and collected vascular risk factors and immunological indicators of patients to elucidate the possible etiologies of UPVD.

The results of the present study indicated that nearly half (48.7%) of the patients with UPVD had abnormal findings on 3D-FLAIR MRI. Berrettini *et al.* (17) reported that the rate of positive findings on 3D-FALIR images was 57% in patients with SSHL, while Lee *et al.* (18) found that 27% of patients with SSHL had positive findings on MRI. Pyykkö *et al.* (19) showed that the positive rate of EH detected by MRI was 90% in patients with MD. In a study of Byun *et al.* (20), 69% of the patients with acute UPVD exhibited enhancement of the vestibular nerve on 3D-FALIR images. However, the enhancement of the vestibular nerve was not observed in a study conducted by Eliezer *et al.* (21). From the abovementioned findings, it can be seen that the rate of positive findings on 3D-FALIR MRI in patients with UPVD varies. This may be related to the differences in participants included and the stages of disease among the different studies. Further studies with larger sample size are needed to confirm our findings.

In the present study, we found that patients with UPVD are more likely to show abnormal imaging findings, with cutoff values of PTA and CP of 32 dB and 46.5%, respectively. A previous study reported that patients with UPVD mostly have abnormal audiological test results, and patients with SSHL had a hearing loss of 30 dB or more over at least 3 consecutive frequencies within 72 hours (22). MD is a cochleovestibular disorder associated with EH and is characterized by fluctuating hearing loss and vestibular symptoms (23). Patients with labyrinthitis may also experience hearing loss and vestibular dysfunction due to the invasion of bacterial toxins into the labyrinth. In the present study, patients with UPVD were more likely to have abnormal MRI findings of the labyrinth when their mean PTA threshold was greater than 32 dB and their CP value was greater than 46.5% in the caloric test, suggesting that cochleovestibular function tests can help predict abnormal imaging findings in patients with UPVD.

Cochleovestibular function tests in patients with vestibular EH, cochlear EH, vestibular PE, and cochlear PE

Changes in PTA in patients with cochlear PE, vestibular EH, and cochlear EH

In the present study, we found that PTA was higher in patients with cochlear PE than in patients with vestibular

and cochlear EH. Vestibular and cochlear PE are also important parameters in the grading method proposed by Bernaerts (13). A different study showed that both T1-weighted and FLAIR MRI were negative in patients with idiopathic SSHL, but high signal on postcontrast delayed 3D-FLAIR MRI often indicated BLB disruption (24). However, in the present study, the presence of vestibular PE was noted in 9 patients, and all of these patients had isolated PE without the presence of EH. The isolated finding of PE might indicate an underlying pathophysiological process other than hydropic ear disease in patients with UPVD. In a recent development, transmission electron microscopy analysis of capillaries in the interstitium of normal human utricle have been shown capable of revealing different ultrastructural pathological changes in specimens obtained from patients with MD, suggesting that permeability changes in BLB may be one of the main causes of EH. However, it should be noted that histopathological studies are necessarily limited to severe intractable stage IV MD with severe hearing impairment (25). Patients with UPVD included in the present study had not yet exhibited the degree of EH seen in severe intractable stage IV MD. In addition, the study of de Pont *et al.* (26) showed that impairment of BLB in patients with MD was correlated with the grades of EH. Therefore, we speculate that after a long-term follow-up period, EH combined with PE may become apparent in these patients with UPVD. We also surmise that isolated PE may have a different pathophysiological process from that of EH. It is well known that the labyrinthine artery branches from the anterior inferior cerebellar artery to supply blood to the labyrinth, while the anterior vestibular artery and the common cochlear artery branch from the labyrinthine artery, with the common cochlear artery then dividing into the cochlear branches and posterior vestibular artery (27). Therefore, unlike patients with fluctuating auditory symptoms typical of EH, when patients develop isolated labyrinthine infarction (i.e., infarction involving the labyrinthine artery or the common cochlear artery), they often present with symptoms of acute auditory and vestibular involvement due to sudden vascular embolism and have more severe hearing loss than do those patients with EH. Wang *et al.* (28) showed that the higher the asymmetry ratios of the cochlea, vestibule, and vestibulocochlear nerve are, the worse the prognosis of hearing loss in patients with idiopathic SSHL. A meta-analysis conducted by Lammers *et al.* (29) showed that patients who showed high signal intensity on 3D-FLAIR images had poorer hearing, and their final PTA was more than 20 dB worse than that of patients with negative 3D-FLARI MRI. Therefore, 3D-FLARI MRI plays an important role in the diagnosis of UPVD and should be applied promptly when acute severe hearing loss and vestibular symptoms occur in patients. If BLB destruction is observed, patients should be urgently treated to salvage their hearing.

Correlation of EH degree with PTA

In the present study, we also found that vestibular and cochlear EH grades were positively correlated with the degree of PTA. Many previous studies have reported a correlation of vestibular and cochlear EH grades with and PTA. Sepahdari *et al.* (8) investigated the ratio of the area of endolymphatic space in the vestibule and found that EH severity was positively correlated with the degree of hearing loss. Sluydts *et al.* (10) showed that mid- and low-frequency PTAs were both significantly higher in patients with vestibular EH grade III than in those with vestibular EH grade 0; although there was no statistical significance between the different grades of cochlear EH, PTA was higher in patients with cochlear EH grade II than in those with cochlear EH grade I. Zhang *et al.* (30) also confirmed a significant correlation between hearing thresholds at low- and mid-frequency and the grades of the cochlear and vestibular EH, suggesting that the grades of EH in patients with MD can be used to predict the degree of hearing loss. However, our study is different from previous studies in that its objective was to reveal the presence of isolated vestibular EH grade I (isolated saccular hydrops) in some patients. This result is inconsistent with the findings from a previous study showing that EH occurs first at the cochlear apical turn (31). Since endolymph-producing dark cells are mainly distributed in the cochlear canal, utricle, and ampulla and are less abundant in the saccule, Bast's valve near the utricle can inhibit the reflux of endolymphatic fluid from the utricle to the saccule, and as the cochlea is located within close proximity to the saccule, the saccule can act as a reservoir for the endolymph during the early stages of the disease (32). Therefore, we believe that the saccule is the most frequent site for EH formation and should thus be given particular attention during MRI examination.

Correlation of PE and EH degree with CP value

In the present study, we also found that vestibular function impairment was more severe in UPVD patients with PE. The results from vestibular function tests (e.g., CP values on the caloric test) showed that patients with vestibular

PE had significantly higher CP values than did those with vestibular and cochlear EH. Under normal conditions, thermal stimulation can cause a temperature gradient between the 2 segments of the horizontal semicircular canal, thus creating a density difference between the endolymph. The increased hydrostatic pressure of the endolymph under the action of the density difference causes the hair cells in the ampulla to bend, which then induces nystagmus (33). However, in patients with EH, the cross-sectional area of the endolymphatic duct is increased while the volume of endolymphatic duct is expanded, which can cause convection between high- and low-density lymphatic fluids. This counteracts the hydrostatic pressure on the ampulla, weakening the degree of hair cell deflection on the ampulla and caloric test-induced nystagmus, in turn increasing the unilateral CP value (34). However, patients with vestibular PE have significantly greater CP value than do patients with EH. We speculate that this may be due to the vascular embolism involving specific branches of the labyrinthine artery. When specific branches of the vestibular artery are damaged, either the vestibule or the cochlea may be selectively involved, with the involvement of the anterior vestibular artery potentially producing isolated vertigo without hearing loss. The obviously higher CP value on the affected side observed in patients with vestibular PE may be due to severe damage to the vestibular and horizontal semicircular canal hair cells caused by embolization of the anterior vestibular artery. In contrast, patients with EH may have less severe hair cell damage compared to patients with PE, the hair cells on the ampulla may still be deflected, and symptoms associated with EH may fluctuate, with long disease duration. Patients with EH may adopt dynamic vestibular compensation through sensory substitution and behavioral substitution to gradually alleviate lesions on the affected side (35), and so these patients might have showed a lower CP than did patients with vestibular PE.

Correlation of PE and EH degree with vHIT gains

Studies have shown that the crista ampullaris of the semicircular canal contains both type I and type II hair cells, which receive regular and irregular nerve afferent discharge. Type I hair cells are sensitive to high frequency (vHIT) stimulation, while type II hair cells are sensitive to low frequency (caloric test) stimulation. Damage to different types of hair cells can result in selective abnormalities in vestibular function tests (34). Therefore, in patients with PE, if all types of hair cells are severely damaged due to vascular occlusion or inflammation, the vHIT gains may are markedly reduced. Meanwhile, in contrast to EH dissipating the hydrostatic force across the cupula by generating local convective flow, the responses to caloric stimulation would be diminished in patients with PE, with vHIT stimulation depending on the radius of the curvature of the semicircular canal. The radius of curvature of the semicircular canal does not increase when EH occurs, so dynamic responses during vHIT would be largely unaffected (36). Moreover, vHIT is a type of high-frequency stimulation, while the caloric test involves low-frequency stimulation. People's daily life activities are mostly high-frequency activities. However, patients with PE have a shorter course of disease and more persistent symptoms than do those with EH, and thus patients with PE are unable to restore the high-frequency VOR of the semicircular canals in daily activities, showing lower vHIT gains when compared to patients with EH.

Correlation between EH grades and vestibular function

Vestibular function does not seem to be correlated with the grades of vestibular and cochlear EH. A study conducted by Kahn *et al.* (9) revealed no correlation between vHIT gain and saccular hydrops, VEMPs and ampullar hydrops. Similar findings were obtained by Jerin *et al.* (37) showing that the degree of vestibular and cochlea EH were not correlated with CP value. In contrast, a study by Sluydts *et al.* (10) found that patients with vestibular EH grade I had significantly higher CP value than those with vestibular EH grades 0, II and III. It can be seen that results of correlations between vestibular function and grades of vestibular and cochlear EH varies among studies. We speculate that this may be due to the long course of the disease in patients with EH, and the severity of EH fluctuates over a few days or months, which affects the vestibular function of patients, but the magnitude of the fluctuation cannot be identified on MRI. Therefore, the duration of patients' symptoms and the time interval between vestibular evaluation and MRI may also affect the correlation between EH grade and vestibular function outcome.

Etiologic analysis of patients with EH and PE

We further analyzed the possible etiologies of UPVD based on the characteristics of patients with EH and PE. The results showed that 88.9% of patients with PE and 42.9% of patients with EH had vascular risk factors and that the prevalence of vascular risk factors was significantly higher in patients with PE than in patients with EH. It is well known that there is a significant correlation between vascular risk

factors and age, with older patients being more likely to have vascular risk factors. In the present study, patients with PE were on average younger compared to patients with EH, and thus the confounding effect of age on vascular risk factors could be ruled out. Studies have shown that the stria vascularis is a highly specialized and vascularized tissue that lines the lateral wall of the cochlea and plays an important role in maintaining the dynamic balance of endolymphatic fluid and generating cochlear potentials. Additionally, the stria vascularis is one of the important BLBs, and the tight junctions of blood capillaries in the stria vascularis form the morphological site of the BLB that prevent the entry of substances from the blood into the inner ear fluid (38,39). Microvascular changes such as thickening of the vessel wall and reduction in the number of vessels can cause damage to the BLB (39). A cross-sectional study of 160 patients with acute UPVD conducted by Oron *et al.* (40) showed that the prevalence of vascular risk factors were significantly higher in patients with acute UPVD than in the general population, and there was a significant correlation between patients' age and the number of vascular risk factors, suggesting that labyrinthine ischemia caused by small blood vessel occlusion may contribute to the development of vestibular symptoms. Chung *et al.* (41) investigated the clinical significance of cardiovascular factors, including arterial stiffness and metabolic syndrome scores, in the development of acute UPVD and found that arterial stiffness and high metabolic syndrome scores were associated with the development of acute UPVD. Therefore, we hypothesize that when patients have vascular risk factors, they tend to be more susceptible to developing the abovementioned lesions, thus leading to the occurrence of PE as detected by 3D-FALIR MRI. Additionally, we also compared the related clinical symptoms between patients with EH and PE. The results suggest that SN without fixation is more common in patients with PE than in patients with EH. Previous studies indicate that patients with acute UPVD and SN are older and more likely to have cardiovascular risk factors (42), which is consistent with our findings showing SN in PE to be more common and associated with vascular risk factors.

Additionally, our findings also suggested that autoimmune abnormalities may be associated with EH. Lobo *et al.* (43) conducted 3D-FLAIR of the temporal bone in 17 patients with autoimmune inner ear disease and found the presence of EH in 12 (70.6%) patients. EH is the main histopathological feature of MD. Nacci *et al.* (44) compared the differences in thyroid gland functional status and thyroid autoantibodies, including serum thyroid stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), TPO-Ab, Tg-Ab, anti-TSH receptor antibody (TR-Ab) between patients with MD and acute UPVD without audiological impairment and healthy participants, reporting that 60% of patients with MD had 1 or more types of elevated serum autoantibody levels, with an association between MD and autoimmune abnormalities being established. The authors hypothesized that the immune system may play a role in the pathogenesis of MD. In the present study, immunological indicators were positive in 35.7% of patients with EH and 11.1% of patients with PE, although no statistical difference was found between patients with EH and PE; however, the prevalence of immune abnormalities was higher in patients with EH than in those with PE. We speculate that vascular risk factors may be involved in the development of PE, while EH may be associated with autoimmune abnormalities.

Conclusions

In this study, nearly half of the patients with UPVD had abnormal findings on postcontrast delayed 3D-FLAIR MRI, and patients were more likely to show abnormal imaging findings when the cutoff values of PTA and CP values were 32 dB and 46.5%, respectively. The severity of EH in patients with UPVD was positively correlated with the severity of hearing impairment. Hearing impairment and vestibular dysfunction were more severe in UPVD patients with PE compared with those with EH, and this may be related to vascular damage.

Acknowledgments

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-1268/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee

of Aerospace Center Hospital (Peking University Aerospace School of Clinical Medicine; No. 2021-ASCH-010). Informed consent was obtained from all patients.

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