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Original research

Imaging endolymphatic space of the inner ear in vestibular migraine

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ABSTRACT

Background Vestibular migraine (VM), the most frequent episodic vertigo, is difficult to distinguish from Ménière's disease (MD) because reliable biomarkers are missing. The classical proof of MD was an endolymphatic hydrops (EH). However, a few intravenous gadolinium-enhanced MRI studies of the inner ear (*i*MRI) also revealed an EH in VM. The major questions were the frequency and distribution characteristics of EH in VM for diagnostic use.

Methods In a prospective case-control study of 200 participants, 75 patients with VM (49 females; mean age 46 years) and 75 with MD (36 females; mean age 55 years), according to the Bárány and International Headache Society, and 50 age-matched participants with normal vestibulocochlear testing (HP), were enrolled. Analyses of *i*MRI of the endolymphatic space included volumetric quantification, stepwise regression, correlation with neurotological parameters and support vector machine classification.

Results EH was maximal in MD (80%), less in VM (32%) and minimal in HP (22%). EH was milder in VM (mean grade 0.3) compared with MD (mean grade 1.3). The intralabyrinthine distribution was preferably found in the vestibulum in VM, but mainly in the cochlea in MD. There was no interaural lateralisation of EH in VM but in the affected ear in MD. The grade of EH in the vestibulum was correlated in both conditions with the frequency and duration of the attacks.

Conclusion Three features of the *i*MRI evaluation were most supportive for the diagnosis of VM at group and individual levels: (1) the bilateral manifestation, (2) the low-grade EH and (3) the intraaural distribution.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Vertigo attacks in vestibular migraine (VM) and Ménière's disease (MD) are very similar, often undistinguishable and sometimes overlap as subsequent attacks in the same individual—a clinical challenge.
⇒ An endolymphatic hydrops (EH) found by imaging of the inner ear with delayed intravenous gadolinium-enhanced MRI (*i*MRI) was considered to be specific for the diagnosis of MD.
⇒ However, a few small case series described EH in patients with VM, new findings with unclear importance.

WHAT THIS STUDY ADDS

⇒ This study adds quantitative analyses of the frequency and bilateral labyrinthine distribution of EH in patients with VM compared with MD and healthy participants, with evidence that EH can be found in 32% of VM.
⇒ The following imaging characteristics support the diagnosis of VM: a bilateral rather than unilateral manifestation of EH, mild hydrops grades, more commonly located in the vestibulum and less in the cochlea.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The clinical relevance of *i*MRI was demonstrated at the group level by an increase in diagnostic accuracy to separate episodic vertigo attacks in VM from those in MD.
⇒ *i*MRI is clinically relevant for the differential diagnosis of episodic vertigo and thereby determines the therapeutic approach.
⇒ These data stimulate further research on the shared inner ear pathophysiology of VM and MD.

INTRODUCTION

Vestibular migraine (VM) is the most frequent form of episodic vertigo. Of 23 915 patients seen in an outpatient dizziness centre, 11.8% were diagnosed as having VM.[1] In most cases, the clinical features are typical and allow a reliable diagnosis according to the consensus criteria of the International Bárány Society for Neuro-Otology and the International Headache Society.[2] Nevertheless, it is well acknowledged that even experts managing dizzy patients often have difficulties distinguishing between VM and Ménière's disease (MD) because reliable biomarkers are missing.[3 4] The differentiation is especially challenging in patients without specific attendant symptoms, such as headaches in VM or persisting audiovestibular deficits in MD.[5] To complicate matters, VM and MD can show a clinical overlap to the extent of subsequent attacks of both conditions in the same individual.[6 7]

The classical proof of MD was thought to be the in vivo confirmation of an enlargement of the endolymphatic space (ES), in cases with stronger expansions called endolymphatic hydrops (EH).[8] Delayed intravenous gadolinium-enhancement MRI (*i*MRI) of the inner ear was used to analyse

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the severity and lateralisation of EH in patients with MD.[9 10] There were also first studies on an enlargement of the ES and on EH in patients who fulfilled the criteria of VM.[7 11–13] Nevertheless, *i*MRI studies in VM are still too sparse, and earlier imaging studies after intratympanic gadolinium injection are inconclusive for methodological reasons referring to rather small and selective VM patient groups, mostly with persistent auditory symptoms.[12 13]

Because of the clinical relevance, the current prospective case-control study was designed with 200 participants in total, that is, 75 patients with definite VM (dVM) or possible VM (pVM) in comparison to 75 patients with definite MD (dMD) or possible MD (pMD) and 50 age-matched and sex-matched participants (HP) without a history of vertigo or dizziness and with normal vestibulocochlear testing. The focus was on a hitherto lacking imaging analysis of the inner ear's ES in VM, which may serve as a comparative biomarker. The main parameters to be investigated in the study were to (1) determine the frequency of an enlargement of the ES and of the EH, (2) disclose typical patterns of the intralabyrinthine distributions within the cochlea and vestibulum of each ear, (3) weight interaural lateralisation, (4) look for an influence of clinical parameters such as duration, frequency of attacks and severity of auditory and vestibular deficits and (5) look for the influence of disease-independent factors such as age, sex, height and weight. This complex diagnostic approach, including neurotological and neuro-orthoptic assessment, *i*MRI with semiquantitative and volumetric quantification of ES, stepwise regression and support vector machine (SVM) classification, was chosen to establish criteria for reliable differentiation of VM and MD or at least to increase the likelihood of the diagnosis.

METHODS

Patients

This prospective monocentric case-control study examined 200 participants: 75 patients with VM, 75 patients with MD and 50 participants with normal audiovestibular testing (HP). The diagnostic criteria of the Bárány Society and the respective international specialist societies were used for VM[2] and MD.[14] 50 age-matched and gender-matched consecutive inpatients of the Neurology Department without vertigo or dizziness and underlying pathologies of the vestibulocochlear system served as the control group (HP) (online supplemental figure S1). Patients with VM (49 females, 46.4±15.6 years) consisted of 35 dVM (27 females, 44.5±13.7 years) and 40 pVM (22 females, 48±17 years). VM attacks lasted 17.5±25.2 hours, were accompanied by VM typical headaches, sensitivity to light or noise and showed few to no peripheral audiovestibular deficits (table 1; online supplemental tables S1–S3).

Patients with MD (36 females, 55.2±14.9 years) consisted of 35 dMD (14 females, 54.8±14.1 years) and 40 pMD (22 females, 55.6±15.8 years). Attacks lasted 3.2±3.0 hours and were accompanied by MD typical ear symptoms with persisting peripheral audiovestibular deficits in the affected ear. No familial cases of MD were included. For an overview of the groups' pertinent demographic, clinical and diagnostic features, see table 1. Selecting the group of patients with MD, we excluded those who complained about a moderate to severe headache during or immediately after the vertigo attacks with unilateral ear symptoms. On the other hand, patients with pVM and accompanying severe hearing loss were also excluded. This approach seemed to us the most adequate way to separate MD and VM attacks as well as possible and avoid overlap syndromes.

In the following, 'ipsilateral' refers to the clinically leading (or affected) side and 'contralateral' to the opposite (or non-affected) side. If participants presented without a leading clinical side, a pseudorandom number generator was used.[15]

Data were acquired at the interdisciplinary German Center for Vertigo and Balance Disorders and the Neurology Department of the Munich University Hospital, Germany, between 2016 and 2021. Institutional Review Board approval was obtained before the study's initiation (no. 641–15). All participants provided informed oral and written consent in accordance with the Declaration of Helsinki before inclusion in the study.

Table 1 Pertinent demographic, clinical and diagnostic features

	VM	dVM	pVM	MD	dMD	pMD	HP	St
N	75	35	40	75	35	40	50	
Age (in years)	46.4±15.6✦	44.5±13.7●	48.0±17.0‡	55.2±14.9✦	54.8±14.1●	55.6±15.8‡	49.8±15.6 ✦●▲	::
Gender (F:M)	49:26*	27:8●	22:18	36:39*	14:21●	22:18	25:25†	:
Attacks (last 3 months)	8.2±9.4	8.9±8.0	7.7±10.5	14.2±35.7	16.7±47.7	11.9±20.7	–	::
Duration of attacks (in hours)	17.5±25.2✦	17.7±24.5●	17.3±26.0▲	5.0±6.9✦	3.2±3.0●	6.7±8.7▲	–	::
VM- headache	50/75 (66.7%)✦	30/35 (85.7%)●	20/40 (50%)▲	1/75 (1.3%)✦	0/35●	1/40 (2.5%)▲	–	:
History of migraine	36/75 (48%)✦	25/35 (71.4.7%) ●	11/40 (27.5%)▲	1/75 (1.7%)✦	1/35 (2.9%)●	0/40▲	–	:
MD-ear symptoms	3/75 (4%)✦	0/35●	3/40 (7.5%)▲	63/75 (84%)✦	33/35 (94.3%)●	30/40 (75%)▲	–	:
MD ipsilateral	3/75 (4%)✦	0/35●	3/40 (7.5%)▲	61/75 (81.3%)✦	33/35 (94.3%)●	28/40 (70%)▲	–	:
CEMD	24/75 (32%)✦	10/35 (28.6%)●	14/40 (35%)‡	7/75 (9.3%)✦	1/35 (2.9%)●	6/40 (15%)‡	1/50 (2%)‡	:
PEMD	11/75 (14.7%)✦	2/35 (5.7%)●	9/40 (22.5%) *	40/75 (53.3%)✦	21/35 (60%)●	19/40 (47.5%) *	1/50 (2%)✦●▲	:
SVV deviation	8/75 (10.7%)*	1/35 (2.9%)●	7/40 (17.5%)	21/75 (28%)*	12/35 (34.3%)●	9/40 (22.5%)	2/50 (4%)*●†	:
HIT gain ipsilateral<0.8	19/75 (25.3%)*	9/35 (25.7%)●	10/40 (25%)	35/75 (46.7%)*	21/35 (60%)●	14/40 (35%)	3/50 (6%)✦●▲	:
HIT ipsilateral (gain at 60 ms)	0.89±0.16*	0.88±0.14‡	0.89±0.19	0.82±0.19*	0.79±0.20‡	0.84±0.17	0.94±0.09✦●▲	::
HIT AI (%)	6.5±6.8	6.1±6.4	6.9±7.2	8.0±8.1	9.4±9.1	6.8±7.0	5.6±4.8‡	::
CS ipsilateral <5°/s	18/75 (24%)✦	7/35 (20%)‡	11/40 (27.5%) *	37/75 (49.3%)✦	17/35 (48.6%)‡	20/40 (50%) *	0/50✦▲‡	:
CS ipsilateral (°/s)	9.9±6.0✦	10.7±5.2 ●	9.2±6.6	7.6±6.8✦	7.8±7.8 ●	7.4±5.9	15.4±6.3✦●▲	::
CS AI (%)	22.1±19.5✦	23.1±21.5‡	21.3±17.7*	34.7±22.4✦	36.5±23.3‡	33.2±21.6*	11.8±8.9✦●▲	::
PTA MD-typical ipsilateral	0/75✦	0/35 ●	0/40 ▲	41/75 (54.7%)✦	29/35 (82.9) ●	12/40 (30%) ▲	0/40✦●▲	:
PTA LT ipsilateral (dB)	18.1±14.8✦	16.3±10.4●	19.6±17.7▲	41.3±23.7✦	49.9±20.3●	33.7±22.9▲	19.1±10.5✦●▲	::
PTA LT AI (%)	0.2±21.4✦	2.5±21.8●	1.9±21.0▲	28.5±28.9✦	40.0±27.5●	18.4±26.4▲	3.5±16.1✦●▲	::

*Chi-Square test [:], or rank-sum test [::] for VM-versus-MD-versus-HP, where p<0.05, or ♦ if p<0.005.
†Chi-Square test [:], or rank-sum test [::] for dVM-versus-dMD-versus-HP, where p<0.05, or ● if p<0.005.
‡Chi-Square test [:], or rank-sum test [::] for pVM -versus-pMD-versus-HP, where p<0.05, or ▲ if p<0.005.
AI, asymmetry index; CEMD, central eye movement disorder; CS, caloric stimulation; dMD, definite MD; dVM, definite VM; HIT, head impulse test; HP, healthy participant; LT, low tone frequency; MD, Ménière's disease; PEMD, peripheral eye movement disorder; pMD, probable MD; PTA, pure tone audiometry; pVM, probable VM; St, statistical analyses; SVV, subjective visual vertical; VM, vestibular migraine.

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Measurement of the auditory, semicircular canal and otolith functions

Diagnostic workup included a thorough neurological workup (eg, history-taking and clinical examination), neuro-orthoptic assessment (eg, Frenzel glasses, fundus photography and adjustments of the subjective visual vertical), video-oculography during caloric irrigation and head impulse testing, vestibular evoked myogenic potentials, as well as pure tone audiometry (PTA) (online supplemental table S3).

Delayed iMRI of the inner ear

Four hours after intravenous injection of a standard dose (0.1 mmol/kg body weight) of gadobutrol (Gadovist, Bayer), MRI data were acquired in a whole-body 3 Tesla MRI scanner (Magnetom Skyra, Siemens Healthcare) with a 20-channel head coil. A T2-weighted, three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) sequence differentiated endolymph from perilymph. A high-resolution, T2-weighted, spin-echo three-dimensional sampling perfection with application-optimised contrasts by using different flip angle evolutions (3D-SPACE) sequence of the temporal bones delineated the total fluid space (TFS) from the surrounding bone.[15 16]

Semiquantitative (visual) grading of the ES

EH was observed as enlarged negative-signal spaces inside the labyrinth on the 3D-FLAIR images.[17] Semiquantitative visual grading of the ES was performed independently by an experienced head and neck radiologist and two neurologists who were blinded to the clinical data. The ES characterisation was based on a four-point ordinal scale classification (0–3 grade).[15]

3D-(volumetric) quantification of the ES consisted of three steps. First, segmentation of the TFS was based on IE-Vnet (for the method, see Ahmadi *et al*[16]). Second, ES and perilymphatic space were differentiated using volumetric local thresholding (cut-off 6).[18] Third, volumes of cochlea and vestibulum were measured. Normalised ES ratios ($ER\ [\%] = \frac{ES}{TS} \times 100$), that is, ES relative to TFS in per cent, were used for further analyses. Potential sources of demographic group biases (age, gender, height and weight) were corrected using linear regression.

Statistics and validation parameters

Analyses were performed using self-written scripts in MATLAB, V.9.10 (R2021a). Categorical values are reported as the number of cases that fit the category or number of patients in the examined group expressed in (%); ordinal or scalar values are presented as mean±SD. The Wilcoxon rank-sum test 'ranksum.m' was used to examine group differences and group-specific *i*MRI ES patterns, and the signed-rank test 'signrank.m' was used to examine paired differences. Statistics were adjusted for multiple comparisons via false discovery rate (FDR, $q<0.05$). The linear agreement was calculated using the regression analysis '*robustfit.m*'.

Stepwise regression of the ipsilateral ES was used to assess the effect-size proportions (relative r-squared or explained variance) of all disease-specific and non-specific factors, adding extra variance besides group effects. All possible permutations were applied. The median value was used as the representation of the effect-size proportions.

The predictive value of *i*MRI was modelled as SVM classification performance via cross-validation (leaving five participants out for testing and training with the rest) with permutation testing (1000 permutations of labels) and receiver operating characteristic (ROC) curve analysis (using the entire dataset) for each group comparison.

Lateralisation is expressed in two ways. One is the difference between the ipsilateral and contralateral ER (ER, that is, size of ES to TFS in per cent); this expresses how many per cent more of the TFS is additionally occupied by hydrops on the ipsilateral side (positive values) versus contralateral side (negative values). The other measure is the lateralisation index (LI), which is LI (%)=100*(ipsilateral−contralateral)/(ipsilateral−contralateral) and expresses how much the hydrops phenomenon is weighted towards the ipsilateral or contralateral ear, ranging from +100% (totally ipsilateral) to 0% (bilaterally equal) to −100% (totally contralateral).

RESULTS

In all groups of the 200 participants, increases in total ES to the extent of hydrops were found in the following order: maximal in patients with MD (MD: 80%, dMD: 89% and pMD: 73%), followed by VM (VM: 32%, dVM: 23% and pVM: 40%) and minimal in HP (22%).

Group-specific frequency and *i*MRI patterns of ES

ES patterns in VM, MD and HP differed in four categories: prevalence, size (grading and volume), lateralisation and their correlation to neurophysiological or clinical features. ES grading and quantification for VM, MD and HP can be viewed in tables 2 and 3. For further patient data, see also online supplemental tables S1–S3.

Frequency

EH was most frequent in MD (MD: 80%, dMD: 89% and pMD: 73%) when compared with VM (VM: 32%, dVM: 23% and pVM: 40%, signed-rank test $p<0.005$ vs all MD groups, FDR ($q>0.05$) corrected) or HP (22%, signed-rank test $p<0.005$ vs all groups, FDR ($q>0.05$) corrected) (figures 1 and 2; tables 2 and 3).

Size and pattern of intra-aural and interaural distribution of ES

With respect to the ipsilateral ear, semiquantitative visual grading showed higher values for MD (MD: 1.21, dMD: 1.36 and pMD: 1.07) compared with VM (VM: 0.3, dVM: 0.23 and pVM: 0.36) and HP (0.18). The 3D volumetric quantification—that is, ER relative to TFS (ER (%))—of the *ipsilateral* total inner ear and *vestibulum* showed significant differences between groups (MD: 6.1%, dMD: 6.7%, pMD: 5.4%; VM: 4.1%, dVM: 4.1%, pVM: 4.1% and HP: 3.3%) (rank-sum test, FDR ($q<0.05$) corrected) for dMD versus pMD (dVM, pVM and HP) and dVM versus pVM (and HP). No significant difference was found between the dVM and pVM groups. With respect to the cochlea, MD had larger ER% values than VM and HP, with the VM and HP groups being roughly equal in size (figure 1; tables 2,3). VM showed slightly higher grades and volumes in comparison to HP. No significant differences were found on the contralateral side of all three groups.

Lateralisation

The difference between the ipsilateral and contralateral ER showed a transaural lateralisation of EH to the affected ear, which was only significant for patients with MD (MD: 15.6% dMD: 20.8% and pMD: 11%) (signed-rank test, FDR ($q<0.05$) corrected), but not for patients with VM (VM: 2.1%, dVM: 1.5% and pVM: 2.5%) and HP (0.5%) (figures 1,2). Within the inner ear, the vestibulum was more lateralised as compared with

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Table 2 Ipsilateral endolymphatic space quantification for the inner ear (IE), cochlea (C) and vestibulum (V)

			VM	dVM	pVM	MD	dMD	pMD	HP
IE	SQ	EH	23/75 (30.7%)✦	8/35 (22.9%)●	15/40 (37.5%)▲	60/75 (80%)✦	31/35 (88.6%)●	29/40 (72.5%) ▲	11/50 (22%)✦●▲
		Grade	0.30±0.39✦	0.23±0.42●	0.36±0.35▲	1.21±0.86✦	1.36±0.79●	1.07±0.9▲	0.18±0.33✦●▲
		AI (%)	31.7±44.3✦	23.8±42.5●	38.6±45.3	44.5±37.9✦	48.1±36.2●	41.3±39.6	22.7±40.1✦●▲
	3D	ES (mm^3)	11.4±4.2✦	11.2±3.6●	11.6±4.6▲	16.8±6.9✦	19.0±7.3●	15.0±5.9▲	8.9±2.4✦●▲
		ER (%)	4.1±1.4✦	4.1±1.2●	4.1±1.7▲	6.1±2.3✦	6.8±2.4●	5.5±2.1▲	3.3±0.83✦●▲
		ER AI (%)	2.18±16.1✦	1.53±13.4●	2.52±18.2▲	15.6±18.4✦	20.8±19.0●	11.0±16.9▲	0.5±13.9✦●▲
		TFS (mm^3)	277.3±27.6	273.3±25.3	280.8±29.3	275.7±29.2	276.9±26.8	274.8±31.5	269.3±30.1
C	SQ	EH	15/75 (20%)✦	6/35 (17.1%)●	9/40 (22.5%)▲	51/75 (68%)✦	27/35 (77.1%) ●	24/40 (60%) ▲	7/50 (14%)✦●▲
		Grade	0.26±0.42✦	0.19±0.39●	0.34±0.44▲	1.09±0.87✦	1.26±0.78●	0.94±0.93▲	0.14±0.35✦●▲
		AI (%)	23.6±42.0✦	17.1±38.2●	23.3±40.1‡	47.1±44.6✦	51.8±44.7●	42.9±44.6‡	18.0±38.8✦●▲
	3D	ES (mm^3)	3.3±1.5✦	3.2±1.4●	3.4±1.5	4.9±2.9✦	5.7±3.0●	4.2±2.6	2.7±1.5✦●▲
		ER (%)	3.4±1.4✦	3.3±1.3●	3.4±1.5▲	5.1±2.7✦	5.8±2.8●	4.4±2.5▲	3.1±1.3✦●▲
		ER AI (%)	1.63±22.6*	4.01±22.3	0.45±23.1	13.7±29.1*	19.3±31.0	8.8±26.8	1.2±21.1*
		TFS (mm^3)	97.4±12.3	96.6±11.4	98.2±13.1	95.2±12.2	96.7±12.3	93.9±12.2	86.9±15.3
V	SQ	EH	19/75 (25.3%)✦	8/35 (22.9%)●	11/40 (27.5%) ▲	50/75 (66.7%)✦	27/35 (77.1%) ●	23/40 (57.5%) ▲	8/50 (16%)✦●▲
		Grade	0.33±0.49✦	0.27±0.51●	0.39±0.47▲	1.29±0.97✦	1.46±0.95●	1.15±0.97▲	0.2±0.4✦●▲
		AI (%)	20.4±39.1✦	20.0±40.6●	26.7±43.5‡	44.0±41.7✦	46.7±39.6●	41.8±43.8‡	16.0±37.0✦●▲
	3D	ELS (mm^3)	8.1±3.4✦	8.0±3.0●	8.2±3.8▲	11.9±5.0✦	13.2±5.7●	10.8±4.0▲	6.1±1.9✦●▲
		ER (%)	4.5±1.8✦	4.5±1.6●	4.5±2.1▲	6.6±2.6✦	7.3±2.9●	6.0±2.2▲	3.4±0.9✦●▲
		ER AI (%)	1.96±17.7✦	0.26±15.4●	3.9±19.6▲	16.5±19.7✦	20.2±21.2●	13.1±17.9▲	2.2±18.4✦●▲
		TFS (mm^3)	180.5±18.8	178.1±16.7	182.7±20.4	179.9±20.1	178.6±17.6	181.0±22.2	182.2±20.7

*Rank-sum test for VM-versus-MD-versus-NVNP, where p<0.05, or ✦ if p<0.005.
†Rank-sum test for dVM-versus-dMD-versus-NVNP, where p<0.05, or ● if p<0.005.
‡Rank-sum test for pVM-versus-pMD-versus-NVNP, where p<0.05, or ▲ if p<0.005.
AI, asymmetry index; C, cochlea; 3D, three-dimensional, or volumetric quantification of the ELS (mm^3); dMD, definite MD; dVM, probable VM; EH, endolymphatic hydrops; ELS, endolymphatic space; ER, endolymphatic ratio, or ELS/TLS (%); HP, participants with normal vestibulocochlear testing; IE, inner ear; MD, Ménière's disease; pMD, probable MD; pVM, probable VM; SQ, semiquantitative or visual quantification of the ELS following a four-point ordinal scale classification; TFS, total fluid space; TLS, total lymphatic space; V, vestibulum; VM, vestibular migraine.

the cochlea. Here, only dMD showed a side difference (signed-rank test, FDR (q<0.05) corrected).

Correlation of imaging data to clinical and neurophysiological features

MD ipsilateral cochlear ES correlated with the lower tone frequencies of PTA (correlation coefficient 0.551, p<0.001, FDR (q<0.05) corrected) (figure 3A). VM showed no such correlation (correlation coefficient −0.063, p>0.05, not significant) (figure 3B). The vestibular ES of the ipsilateral ear in dMD and dVM correlated with the ranked number of attacks in the 3 months prior to *i*MRI (dMD correlation coefficient 0.536, dVM correlation coefficient 0.602, p<0.001, FDR (q<0.05) corrected) (figure 3C,D), but not the total number of attacks during the course of the condition.

ES-influencing factors

Ipsilateral ES size, ER (%) and variance effect-size proportions were influenced by many factors beyond group effects. A group-specific overview of the stepwise regression results can

Table 3 Contralateral ES quantification

			VM	dVM	pVM	MD	dMD	pMD	HP
Inner ear	SQ	EH	17/75 (22.7%)✦	6/35 (17.1%) ●	11/40 (2.5%)	49/75 (65.3%)✦	24/35 (68.6%) ●	25/40 (62.5%)	12/50 (24%)✦●▲
		SQ (grade)	0.27±0.47✦	0.15±0.31●	0.37±0.56‡	0.68±0.59✦	0.68±0.59●	0.68±0.61‡	0.2±0.31✦●‡
	3D	ELS (mm^3)	11.1±4.6	10.9±3.6	11.2±5.3	11.6±3.6	11.6±3.5	11.7±3.7	8.9±2.4✦●▲
		ER (%)	4.0±1.4	4.0±1.2	4.0±1.6	4.2±1.1	4.2±1.1	4.2±1.1	3.3±0.8✦●▲
		TFS (mm^3)	276.8±26.8	272.7±24.7	280.3±28.4	276.5±31.2	277.3±30.0	275.8±32.5	268.3±26.0
Cochlea	SQ	EH	12/75 (16%)✦	4/35 (11.4%)†	8/40 (20%)	31/75 (41.3%)✦	11/35 (31.4%)†	20/40 (50%)	10/50 (20%)▲*
		SQ (grade)	0.21±0.47✦	0.14±0.36●	0.28±0.54▲	0.63±0.70✦	0.59±0.73●	0.66±0.67▲	0.2±0.4✦●▲
	3D	ELS (mm^3)	3.3±1.5	2.9±1.4	3.5±1.9	3.4±1.6	3.6±1.8	3.3±1.3	2.7±1.2*†‡
		ER (%)	3.2±1.4	3.0±1.3	3.4±1.5	3.6±1.5	3.6±1.6	3.5±1.4	3.0±1.3*
		TFS (mm^3)	96.9±13.3	94.3±10.7	99.2±14.9	94.8±13.3	95.9±13.1	93.8±13.6	89.1±11.3*†
Vestibulum	SQ	EH	14/75 (18.7%)✦	4/35 (11.4%)●	10/40 (25%)	39/75 (52%)✦	21/35 (60%)●	18/40 (45%)	12/50 (24%)✦●‡
		SQ (grade)	0.30±0.53✦	0.16±0.36●	0.43±0.63	0.73±0.70✦	0.77±0.65●	0.70±0.76	0.24±0.43✦●
	3D	ELS (mm^3)	8.1±3.5	8.0±2.9	7.8±4.0	8.2±3.1	8.1±2.6	8.4±3.6	6.1±1.9✦●▲
		ER (%)	4.3±1.7	4.5±1.6	4.2±1.9	4.5±1.5	4.5±1.4	4.5±1.6	3.5±1.0✦●▲
		TFS (mm^3)	179.3±18.1	177.4±17.7	180.9±18.5	182.4±20.6	181.3±19.5	183.4±21.7	178.5±19.6

*Signed-rank test for VM-versus-MD-versus-HP, where p<0.05, or ✦ if p<0.005.
†Signed-rank test for dVM-versus-dMD-versus-HP, where p<0.05, or ● if p<0.005.
‡Signed-rank test for pVM-versus-pMD-versus-HP, where p<0.05, or ▲ if p<0.005.
AI, asymmetry index; 3D, three-dimensional, or volumetric quantification of the ELS (mm^3); dMD, definite MD; dVM, probable MD; EH, endolymphatic hydrops; ELS, endolymphatic space; ER, endolymphatic ratio, or ELS/TLS (%); ES, endolymphatic space; HP, participants with normal vestibulocochlear testing; MD, Ménière's disease; pMD, probable MD; pVM, probable VM; SQ, semiquantitative or visual quantification of the ELS following a four-point ordinal scale classification (X); TFS, total fluid space; TLS, total lymphatic space; VM, vestibular migraine.

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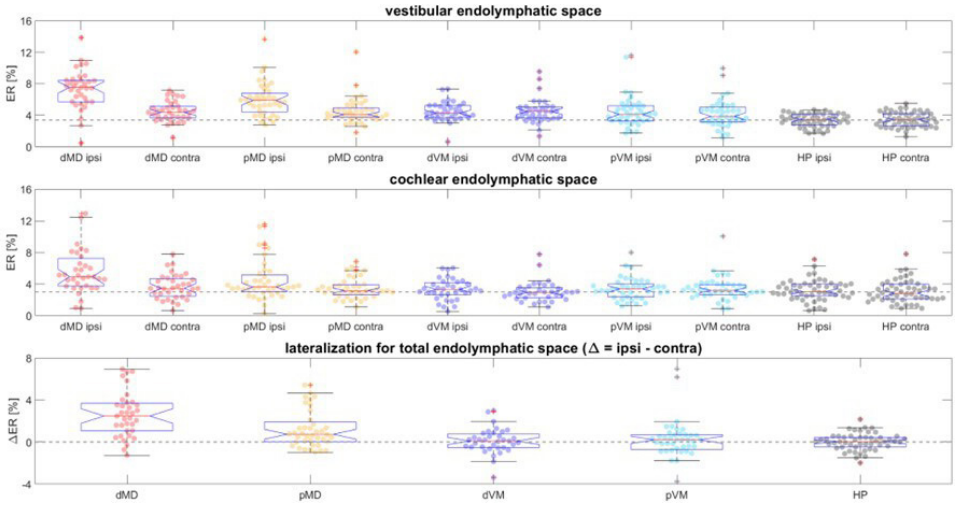

Figure 1 Group-specific ES patterns in VM, MD and HP. Three plots depict colour-coded group-specific normalised volumetric ES results of the vestibulum (upper plot), cochlea (middle plot) and inner ear (lower plot). The x-axis shows the ipsilateral (affected) and contralateral (unaffected) normalised volumetric ES for dVM and pVM (dVM: dark blue and pVM: light blue), MD (dMD: red and pMD: orange) and HP (grey). The lower graph shows the inner ear's ES differences between the ipsilateral and contralateral sides. The higher the value, the more there was lateralisation towards the ipsilateral ES. The y-axis scales the ER (size of ES relative to total fluid space in per cent) in the two upper plots, and ΔER (the difference between ipsilateral and contralateral ER) in the lowest plot. Note that the group-specific ES pattern differed in size and symmetry. While the ES of the MD group (dMD and pMD) was pronounced and lateralised to the affected ear, the ES in the VM (dVM and pVM) and HP groups were less pronounced and not lateralised to one side ($p<0.005$, signed-rank test, false discovery rate ($q>0.05$) corrected). dMD, definite MD; dVM, definite VM; ES, endolymphatic space; ER, ES ratio; HP, participants with normal vestibulocochlear testing and intravenous gadolinium-enhanced MRI; MD, Ménière's disease; pMD, probable MD; pVM, probable VM; VM, vestibular migraine.

be seen in figure 4. Between 19.4% and 20.2% of the variance was explainable by demographic, non-disease-specific factors (such as age, height or weight) (online supplemental table S1). Between 3.8% and 25.1% of the variance was due to deficits registered by neurophysiological parameters, such as caloric irrigation, PTA and video-head impulse tests. Most of the variance (between 15.1% and 32.9%) could be explained by disease-specific factors: ES in VM and MD (although VM>MD) showed a marked relationship to recent disease activity (attacks in the last 3 months, time since the last attack) and attack duration. Furthermore, ES in MD showed the most variance in the deficits of neurophysiological testing results (dMD>pMD).

In HP, most variance was caused by demographic, non-disease-specific factors, while less than a quarter was due to deviations in neurophysiological testing results.

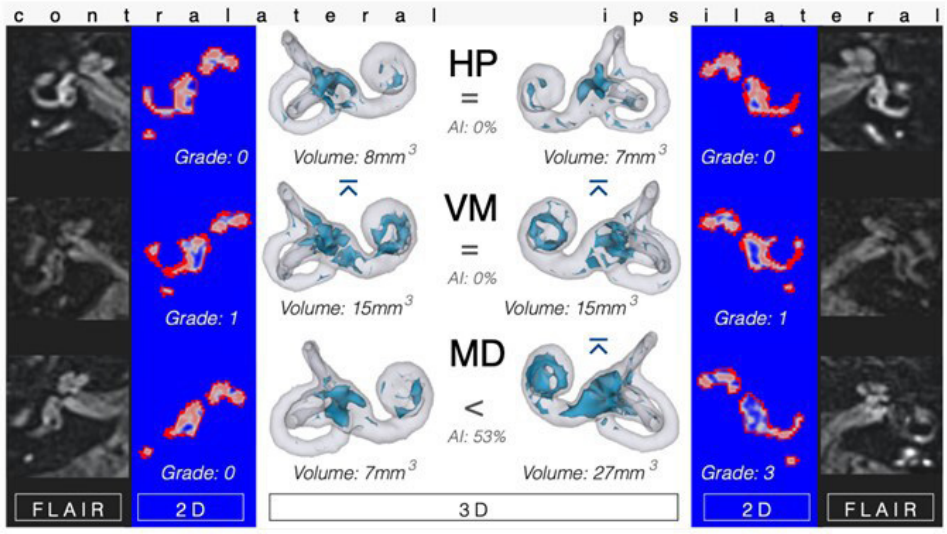

Figure 2 Group-specific 3D-quantification of ES in VM, MD and HP. Ipsilateral (or affected) ears are shown on the right, and contralateral ears are shown on the left side. The asymmetry index (in %) and total volume in both ears are part of the group-specific ES patterns. Each group is depicted in a 2D raw FLAIR sequence (black), in 2D after VOLT processing (blue) and in 3D after VOLT processing (white). 2D, two-dimensional; 3D, three-dimensional; dMD, definite MD; dVM, definite VM; ES, endolymphatic space; ER, ES ratio; FLAIR, fluid-attenuated inversion recovery; HP, participants with normal vestibulocochlear testing and intravenous gadolinium-enhanced MRI; MD, Ménière's disease; pMD, probable MD; pVM, probable VM; VM, vestibular migraine; VOLT, volumetric local thresholding.

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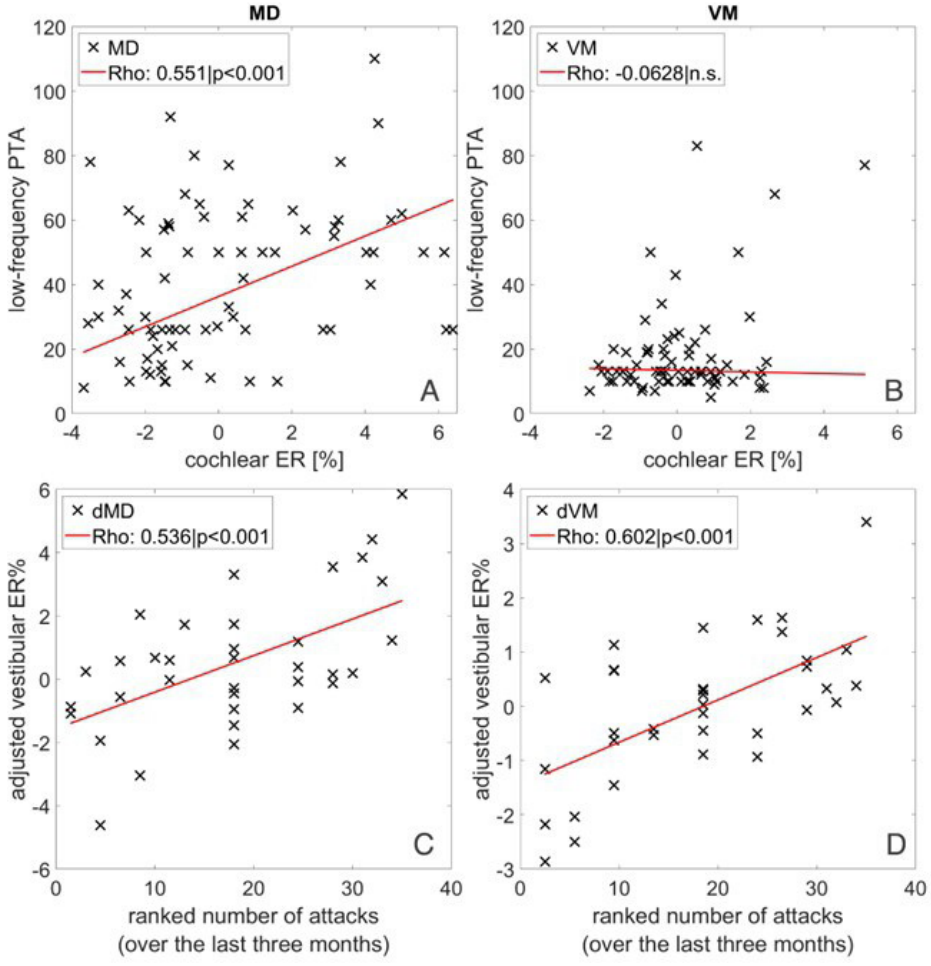

Figure 3 Correlations of ES. In neurophysiological testing, a positive correlation was found between ER (size of ES relative to total fluid space in per cent) in the ipsilateral cochlea and low-frequency pure tone audiometry on the ipsilateral side for MD (A), but not for VM (B). For clinical features, a correlation between ER (size of ES relative to total fluid space in per cent) in the vestibular ES of the ipsilateral ear (affected side) and the ranked number of attacks in the last 3 months before the examination was found (ranked least number of attacks to the most number of attacks using tied rank in MATLAB) (C and D). An overall significant correlation between greater relative ES size and the number of attacks can be observed in dMD (C) and dVM (D). dMD, definite MD; dVM, definite VM; ES, endolymphatic space; ER, ES ratio; HP, participants with normal vestibulocochlear testing and intravenous gadolinium-enhanced MRI; MD, Ménière's disease; pMD, probable MD; pVM, probable VM; VM, vestibular migraine.

*i*MRI predictive value to differentiate VM from MD and HP

All group-specific diagnostic accuracy parameters are depicted in figure 5. Diagnostic accuracy (area under the curve (AUC) in the ROC curve) of *i*MRI modelled as SVM was easiest versus HP (dMD: AUC=0.998, pMD: AUC=0.950 and dVM: AUC=0.898, pVM: AUC=0.903), good when distinguishing between VM and MD (dMD-vs-dVM: AUC=0.957 and pMD-vs-pVM: AUC=0.946) and harder between probable diagnoses (pMD-vs-dVM: AUC=0.892 and dVM-vs-pVM: AUC=0.749) (figure 5). Features with the highest weight (top three positive and bottom three negative weights in each classification) of the SVM classification were mainly assigned to the side differences in ER (%) and asymmetry indices for the vestibulum, inner ear and cochlea (with most weight on the vestibular differences), followed by the ipsilateral and contralateral ER (%) sizes of the vestibulum, cochlea and inner ear. Hence, side differences were most useful for classification (analogue to the pattern in figure 1), followed by the 'absolute' size of ES (MD>VM>HP).

DISCUSSION

The current MRI study of the inner ear has shown that significant enlargements of the ES to the extent of hydrops occur with different frequencies in all three groups: most frequent in MD (80%), less in VM (32%) and HP (22%). The high prevalence of EH has been proven for MD in numerous inner ear imaging studies using different gadolinium-enhanced MRI methods (for review, see Connor *et al*).[9] However, in patients with VM, EH is a relatively new finding. It has been described in a few studies[7 13 19] and in some patients presenting with both entities, MD and VM.[7] Even age-matched healthy controls showed a low percentage of EH with a low grade.[20 21] Therefore, the long-held belief that an EH is a pathognomonic finding in MD was questioned.[22] Thus, imaging of the inner ear used nowadays requires additional diagnostic criteria, which we used in the current study, such as the distribution and grading of EH in patients with episodic vertigo. We regard the latter criteria as all the more important than other typical clinical and neurophysiological features.

The following imaging characteristics could be elaborated on. First, about one-third of patients with VM exhibited an EH that was milder (mean grade 0.3) on a four-point scale from 0 to 3[15 18] as compared with that found in MD (mean grade 1.3). Second, the intralabyrinthine distribution of EH in VM was preferably found in the vestibular part of the labyrinth, while the cochlea was mainly affected in patients with MD. Third, there was no

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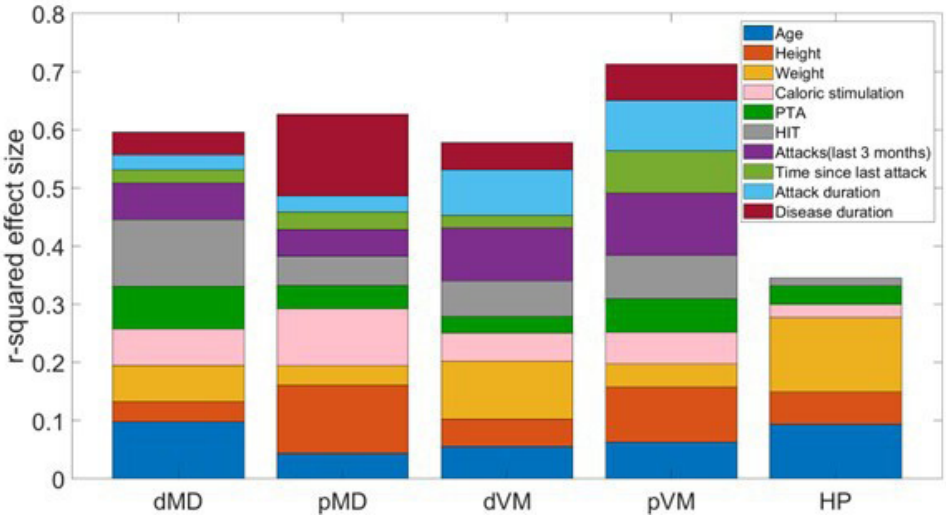

Figure 4 Influencing factors of ES. Stepwise regression was used to assess the effect-size proportions of disease-specific and non-specific factors adding variance to the ipsilateral normalised ES (ER (%)) for dVM and pVM and MD (dMD and pMD) or participants with normal audiovestibular testing (HP). The y-axis shows the r-squared effect size (from 0 to 0.8). The x-axis shows the colour-coded explained variance for each factor (view colour attribution in the legend) per group. The ipsilateral ES size variance was explained by three categories of factors. The first category was non-specific demographic factors, unrelated to disease (such as age, height and weight). The second category was factors derived from neurophysiological testing, such as caloric irrigation response (caloric stimulation), PTA and HIT. The third category was factors related to disease, such as number of attacks, time since last attack, disease duration and average attack duration. dMD, definite MD; dVM, definite VM; ES, endolymphatic space; ER, ES ratio; HIT, head impulse test; HP, participants with normal vestibulocochlear testing and intravenous gadolinium-enhanced MRI; MD, Ménière's disease; pMD, probable MD; pVM, probable VM; PTA, pure tone audiometry; VM, vestibular migraine.

interaural lateralisation in VM, but a distinct lateralisation of the affected ear was typical for MD. Fourth, the grade of the EH in the vestibular part of the labyrinth correlated in both conditions (dVM and dMD) with the frequency of attacks during the last 3 months before *i*MRI, the time since the last attack and the mean attack duration. In patients with MD, EH of the cochlea correlated with the deficits of lower tone frequencies in pure tone audiometry; neurophysiological deficits of vestibular function (semicircular canal and otolith) also occurred mostly in MD (dMD>pMD). The latter findings support earlier studies in patients with MD.[23–26] Fifth, disease-independent factors such as age, height or weight were responsible for 19%–20% of the variance according to the SVM classification. Hence, based on our imaging data, three features were most supportive for the diagnosis of VM at the group and individual levels: (1) the *bilateral* manifestation of EH; (2) the *low-grade* EH, as opposed to the mandatory asymmetry with a higher-graded EH of the affected ear in patients with MD and (c) the intra-aural distribution, preferably located in the *vestibulum* in VM but most pronounced in the cochlea rather than the vestibulum in MD. These criteria for differentiation demonstrate that semiquantitative and, more precisely, volumetric quantification of the ES is helpful for the analyses of delayed *i*MRI of the inner ear. In other words, a pronounced interaural lateralisation of a higher-grade EH or an intra-aural accentuation within the cochlea argues against a VM.

In the current *i*MRI study, when modelled as an SVM, ES side differences and size were weighted most usefully to classify VM, MD and HP. Diagnostic accuracy was highest (AUC=0.998) when differentiating VM and MD from HP and lowest when differentiating dVM from pVM (AUC=0.749; figure 4). Two previous studies applied a predictive model.[26 27] Liu and colleagues[27] used clinical measures[2 14] in a multivariable double logistic regression analysis and regression equation to retrospectively differentiate 110 VM from 110 patients with MD. The methods did not allow the variables to be determined. Variables were selected (with univariate χ^2 tests) without explicit restriction to the training data in each cross-validation fold. Ito and colleagues[26] used multivariate logistic regression analysis just to differentiate unilaterally patients with dMD from healthy volunteers. The lower specificity (0.94) and sensitivity (0.83) could be explained by the lack of separation between the affected (ipsilateral) and contralateral sides.

How can a mild bilateral EH in VM be explained? We think that one possibility is a transient relapsing ischaemia in the labyrinth that causes an EH and consequently Ménière-like symptoms, which often occur in association with VM and exceed those of the normal population.[28 29] This would be in agreement with the finding of variations in the hydrops degree depending on the time interval from the last attack[19] and the frequency of VM attacks during the last 3 months prior to the *i*MRI found in our study. What may induce transient ischaemia? There is evidence that the trigeminal nerve plays an important role in VM and its involvement in the inner ear. It was shown that the trigeminal nerve provides a dense sensory innervation of cerebral, basilar and meningeal blood vessels and thus of the vascular supply of the inner ear via the anterior inferior cerebellar artery (AICA). Indeed, the cochlea and the vestibular labyrinth receive trigeminal innervation via the ophthalmic branch, which provides parasympathetic innervation to the basilar artery and the AICA.[30–32] Activation of perivascular trigeminal nerve endings causes the release of substance P and calcitonin gene-related peptide, leading to local neuroinflammation, permeability changes, vasodilatation and oedema.[33 34] Thus, the trigeminal nerve directly affects neuroinflammation and blood flow in the inner ear.

It should be noted that this VM hypothesis was not the subject of the present investigation but remains to be investigated in further studies. This is also true for the recent discovery of various clinical and molecular subgroups of MD based on heritability and proinflammatory cytokines (for review, see Frejo and Lopez-Escamez[35]). The message of our imaging data is

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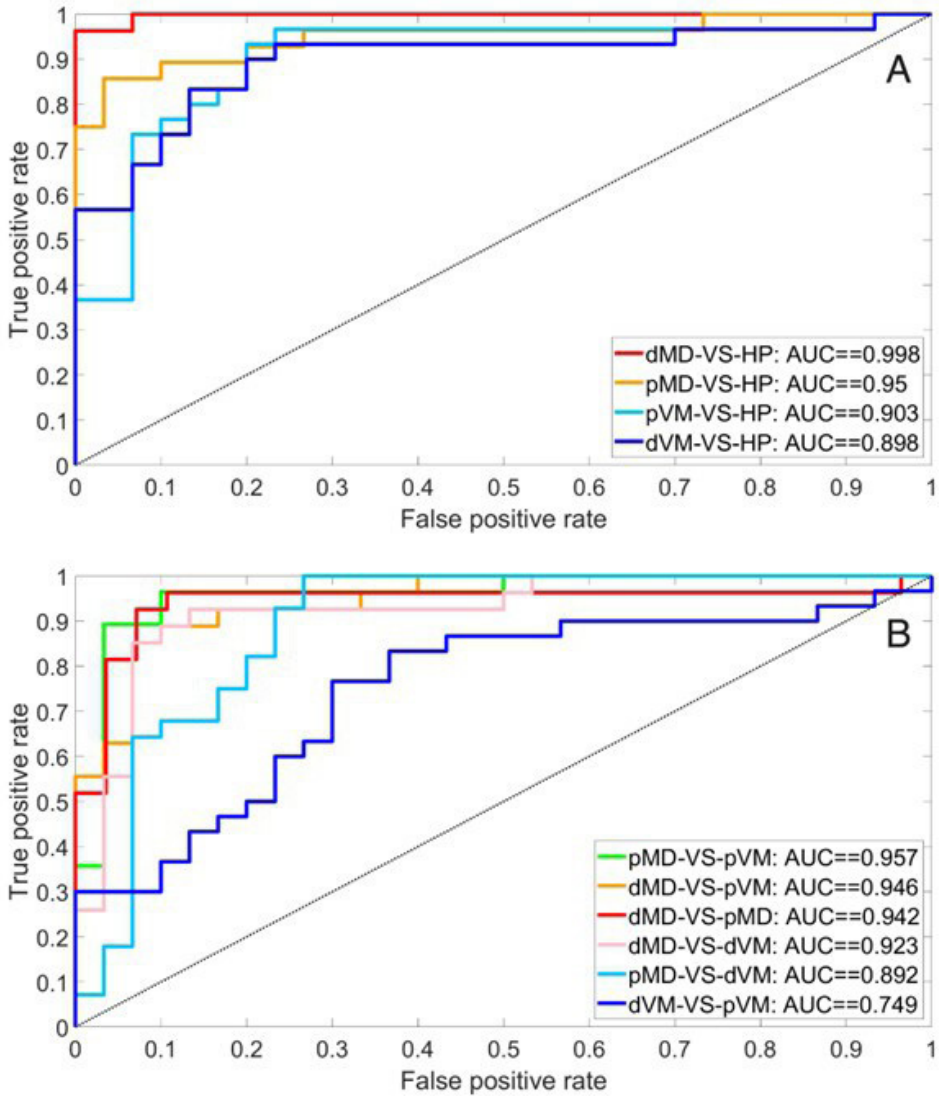

Figure 5 Clinical intravenous gadolinium-enhancement MRI predictive value to differentiate VM from MD and HP. Classification accuracy is shown via the ROC curve (true positive rate plotted over the false-positive rate) and AUC for dVM and pVM and MD (dMD and pMD). (A) The discriminative power versus participants with normal audiovestibular testing (HP). (B) The discriminative power of the VM and MD groups versus each other. AUC, area under the curve; dMD, definite MD; dVM, definite VM; ES, endolymphatic space; ER, ES ratio; HP, participants with normal vestibulocochlear testing and intravenous gadolinium-enhanced MRI; MD, Ménière's disease; pMD, probable MD; pVM, probable VM; ROC, receiver operating characteristic; VM, vestibular migraine.

the improvement of diagnostic accuracy by combining clinical, neurophysiological and structural inner ear imaging data.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. Institutional Review Board approval of the Ludwig-Maximilians University, Munich, Germany, was obtained before the study's initiation (no. 641-15). Participants gave informed consent to participate in the study before taking part.

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