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ORIGINAL COMMUNICATION

# Clinical, oculographic and vestibular test characteristics of Ménière's disease

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## Abstract

Seventy Ménière's disease (MD) patients with spontaneous vertigo (100%), unilateral aural fullness (57.1%), tinnitus (78.6%), and subjective hearing loss (75.7%) self-recorded nystagmus during their episodes of vertigo using portable video oculography goggles. All demonstrated ictal spontaneous nystagmus, horizontal in 94.3% ($n=66$) and vertical in 5.7% ($n=4$), with a mean slow-phase velocity (SPV) of 42.8 ± 31.1°/s (range 5.3–160.1). Direction reversal of spontaneous horizontal nystagmus was captured in 58.6%, within the same episode in 34.3%, and over different days in 24.3%. In 18.6%, we observed ipsiversive then contraversive nystagmus, and in 12.9% contraversive to ipsiversive direction reversal. Ictal nystagmus SPV (42.8 ± 31.1°/s) was significantly faster than interictal (1.4 ± 3.1°/s, $p<0.001$, CI 34.277–48.776). Compared to age-matched healthy controls, interictal video head impulse test gains in MD ears were significantly lower, cumulative and first saccade (S1) amplitudes were significantly larger, and S1 peak velocities were significantly faster ($p=0.038/0.019/0.008/<0.001$, CI 0.002–0.071/0.130–1.444/0.138–0.909/14.614–41.506). Audiometry showed asymmetrically increased thresholds in 100% of MD ears ($n=70$). Significant caloric, air-conducted (AC) cervical vestibular-evoked myogenic potential (VEMP), and AC ocular VEMP asymmetries were found in 61.4, 37.9, and 44.4% of patients (MD ear reduced). Transtympanic electrocochleography tested in 36 ears (23 patients) showed 81.8% of MD ears had a positive result for hydrops (either a summating potential at 1/2 kHz < − 6 µV, or an SP/AP ratio > 40%). Using ictal nystagmus findings of SPV > 12°/s, and a caloric canal paresis > 25%, we correctly separated a diagnosis MD from Vestibular Migraine with a sensitivity and specificity of 95.7% and 85.1% (CI 0.89–0.97).

**Keywords** Ménière's disease · Nystagmus · Endolymphatic hydrops · Video nystagmography · Event monitor

## Introduction

Ménière's disease (MD) is a peripheral vestibular disorder presenting with fluctuating aural symptoms (fullness, tinnitus, and hearing loss), and recurrent spontaneous vertigo lasting between 20 min and 12 h [1]. Although it accounts for only 7.2–7.5% of recurrent vertigo presentations in outpatient facilities, MD constitutes a disabling syndrome [2, 3].

With increasing knowledge of inner ear anatomy, diverse theories on the pathophysiology of MD and events underlying an attack of vertigo have evolved [4, 5]. The '*Reissner's membrane rupture*' theory suggested that an abnormal periodic accumulation of endolymphatic fluid ruptures portions of the membranous labyrinth, causing an outflow of potassium-rich endolymph which then mixes with the perilymph [5–7]. This proposed phenomenon was hypothesised to initially produce an excitation/depolarisation of the primary vestibular afferents with resulting ipsiversive nystagmus (the irritative phase); the subsequent decrease in spontaneous activity was attributed to a saturation of the perilymph fluid with the potassium of the endolymphatic fluid, and a resultant total

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depolarization (the paretic phase) [6, 7]. However, animal and imaging studies have found the membrane rupture theory to be largely unfounded [8–10]. A '*drainage*' or '*physiological valve*' theory for recurrent MD episodes proposes that a build-up of endolymph in the cochlea periodically shunts the fluid into nearby compartments, possibly via the valve of Bast or the endolymphatic sinus, only to gradually accumulate again [9, 11, 12]. Corroborating the important role of the endolymphatic sac and its ability to gatekeep endolymphatic fluid within the ear, studies exist of refractory MD being treated successfully with surgical endolymphatic duct blockage or decompression [10, 13].

While there is no known single gold-standard test for MD, the history of episodic spontaneous vertigo associated with aural symptoms, including low/mid-frequency sensorineural hearing loss, asymmetric vestibular test results, and ictal fluctuating vestibular test results are central in the diagnosis of MD [14–16]. The video head impulse test has allowed investigators to observe a transient increase or reduction in labyrinthine function when measuring vestibulo-ocular gain during an attack of vertigo, which may either return to normal, or greater than normal, post-attack [17, 18]. Other peripheral vestibular changes have been observed during an acute episode of MD, as an enhanced dynamic utricular response from the affected MD ear during the ocular vestibular-evoked myogenic potential test [19]. Transtympanic electrocochleography may also be used to assess the presence of abnormal build-up of endolymphatic fluid within the labyrinth, but is less commonly utilised due to being mildly invasive [20]. Nystagmus during an attack of MD is high in velocity, is most frequently horizontal, and shows spontaneous direction reversal over seconds to hours [6, 21, 22]. These distinctive periods of horizontal direction-reversing nystagmus (*ipsiversive/contraversive/ipsiversive*) during an attack have been named the irritative, paretic (or paralytic), and recovery phases of MD [6, 7, 23, 24]. Downbeating nystagmus has also been observed in cases of bilateral MD [25].

There are several sets of diagnostic criteria used for the classification of MD (*American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS)/Bárány Society*). Some studies have incorporated audiovestibular test results to track disease progression and to help classify the stage of disease [26, 27]. Vestibular test results and examination findings may be a promising addition to current diagnostic criteria [1, 28]. The aim of this study is to describe ictal nystagmus characteristics in MD, track nystagmus evolution over the course of an attack, and to examine the combined utility of ictal nystagmus and interictal audiovestibular test profiles when seeking to separate MD from its common mimic, Vestibular Migraine.

## Methods

### Eligibility criteria

Eligibility criteria for participation in this observational cohort study included adults with a history of recurrent spontaneous vertigo lasting at least 20 min. Patient results included in the final study included those with a final diagnosis of MD, and had conducted ictal video oculography (VOG) at home during an attack of vertigo. Patients were prospectively recruited from an outpatient neurology clinic with written informed consent (August 2014–June 2020). Patients were taught how to record a routine of eye videos on a small, portable VOG device during vertigo [29]. Eligibility criteria for the comparison of Vestibular Migraine (VM) patients included a final diagnosis of VM or probable VM, with ictal video oculography (VOG). Information regarding classification, eligibility and testing parameter of patients with VM can be found in Young et al. [30]. Clinical features of those with VM can be found in Online Resource 1.

### Patient classification

Patients included in this study were treated by specialists unblinded to the patients' ictal home VOG recordings. Final diagnoses were based upon case history, physical examination, imaging where indicated, and audiovestibular test results. Diagnostic classification was based upon those outlined in the *Bárány Society* diagnostic criteria for definite Ménière's disease (MD), probable MD (pMD), and delayed MD (del-MD) (which has formerly been described in the literature as *Delayed (Endolymphatic) Hydrops*) [1, 31]. A classification of MD was made when the following conditions were met: ≥ 2 episodes of spontaneous vertigo lasting between 20 min and 12 h; A low- or mid-frequency sensorineural hearing loss in the affected ear, documented with audiometry; reported subjective fluctuating aural symptoms including tinnitus, fullness, or hearing loss; and not better fitting a different diagnosis. Probable MD was diagnosed when the above criterion was met without a documented audiometric hearing loss. When the vertigo onset was delayed in relation to the hearing loss by weeks to years, and the criteria for MD were then met, a diagnosis of del-MD was given.

### MD nystagmus phase classification

In cases of unilateral MD, while sitting in an upright, gaze-forward position, the *irritative* nystagmus phase is understood to be visible at the earliest stages of an attack, its fast phase beating ipsilesionally towards the affected ear, closely

followed by the *paretic* nystagmus phase which beats away from the affected ear [6, 23]. Lastly, *recovery* nystagmus is thought to reverse a second time and beat towards the affected ear [7]. The term *ictal* refers to the period during an attack of vertigo, and *interictal* is the interval between attacks when the patient does not have vertigo.

## Home video oculography

Vision-denied eye recording goggles were designed and constructed for research patient use [29]. A video camera was attached to the left eye cup of swimmers' goggles with two infrared lights. The right eye cup of the goggles was also blocked of light, and all recordings conducted without fixation. A total of seventy devices were constructed for patient use.

Using the device at home, patients were instructed to conduct a short eye video recording as close as possible to the start of a vertigo attack. The routine involved sitting upright while looking forward with eyes open (primary position), for 15 s. Patients were instructed that if they felt well enough, to continue the recording by lying supine and then in both side-lying (lateral) positions for 30 s each. Patients were advised to verbally describe all positions during the manoeuvres. Patients were advised to make consecutive video recordings every 15 min from symptom onset when possible, verbally indicating the time at the beginning of each recording. After a patient had successfully recorded at least one attack of vertigo with the recording device, patients were advised to return it at follow-up, or to upload the files to an encrypted file-sharing website (University of Sydney). Patients were advised to take any antiemetic medications prescribed before making a video recording.

## Audiovestibular tests

Patients had audiovestibular testing and imaging as deemed appropriate after consideration of case history, or as requested by their referring medical practitioner. As participating in audiovestibular tests was not a pre-requisite for study participation, not all patients received all tests, and total number of patients tested are listed for each test.

Pure-tone audiometry was conducted in all patients, with asymmetry based upon criteria of interaural octave thresholds difference ≥ 20 decibels normal hearing level (dB HL) (ISO) at a single frequency, ≥ 15 dB HL at two frequencies, or ≥ 10 dB HL at three or more frequencies [32]. Bithermal caloric testing [water irrigation; 30° and 44 °C for 25–40 s (s)] was conducted with VOG. Canal paresis (CP) was calculated based on nystagmus slow-phase velocity (SPV) during irrigation, using the Jongkees formula. CP was considered significant if ≥ 25% [33].

Vestibular-evoked myogenetic potential (VEMP) testing was conducted with 64 patients (Natus Medelec Synergy version 20.0, California, USA). Monaural air-conducted (AC) click stimuli and bone-conducted (BC) minishaker taps were used to evoke cervical (c) and ocular (o) VEMPs. AC stimuli were 0.1 ms (ms) monaural clicks at 5/s rate with TDH-49 headphones, using alternating polarity at 105 decibels normal hearing level (dB nHL) (140 dB peak sound-pressure level (SPL)). BC click-taps (1 ms, 20-V amplitude) were delivered using a hand-held 'minishaker' to the midline forehead, at 5 taps/s with condensation polarity (Bruel and Kjaer 4810). VEMP asymmetry ratios (ARs) were compared with age-matched normal control subjects tested with the same equipment and parameters [33]. VEMP reflex parameters are described in peak-to-peak microvolts (μV) for oVEMP. A corrected amplitude (CA) is described for cVEMPs which is a measurement in relation to the baseline sternocleidomastoid muscle activity, and is therefore without unit. Asymmetry ratios for VEMP reflexes and caloric results were calculated using the Jongkees formula.

Lateral video head impulse test (vHIT) was conducted with 66 patients, and 20 had further testing of the anterior and posterior semicircular canal planes (ICS Impulse USB goggles; Otometrics, Taastrup, Denmark). A minimum of 20 head impulses were conducted for each canal, resulting in a vestibulo-ocular reflex (VOR) gain calculation. The mean results of patients with MD were compared against the means (± two standard deviations) of age-matched normal controls [34]. Only lateral vHIT impulses with head velocities between 150 and 250 degrees per second (°/s) were included for analysis. Lateral vHIT saccade analysis was processed and analysed offline with custom software designed by author A.B. (LabView v2012; National Instruments, Austin, TX).

In a select sub-group of patients, trans-tympanic electrocochleography (ECochG) was performed by an Ear, Nose and Throat surgeon under local topical anaesthesia (*phenol*) applied to the tympanic membrane. A thin, stainless steel needle electrode was inserted through the tympanic membrane and placed onto the promontory of the cochlea, within close proximity to the round window [20]. Click [80 dB normal (*n*) HL] and tone-burst (0.5 and 1 kHz at 80 dBnHL, 2 and 8 kHz at 70 dBnHL) stimuli were monaurally presented with a TDH-49 headphone. Responses were recorded on a Natus Medelec Synergy (version 20.0, California, USA). The summating potential versus action potential ratio (SP/AP), and absolute SP to tone-burst stimuli were measured. The cut-off values used to determine a positive hydrops test result were an absolute SP deflection from baseline with an amplitude ≤ − 6 microvolts (μV) to 1 kHz and/or 2 kHz tone-burst stimuli, and/or an SP/AP ratio > 0.4 [20, 35, 36]. Audiovestibular tests were administered interictally unless otherwise indicated.

### Nystagmus analysis

VOG videos (30 Hz) were analysed offline by authors (blinded as to the patients' final diagnosis), using two custom LabVIEW nystagmus analysis programmes (detailed analysis methods can be found in Young et al. [29]). Nystagmus was analysed in horizontal and vertical planes for each individual manoeuvre recorded. Slow-phase nystagmus velocity was determined in degrees per second (°/s). When patients had recorded multiple videos, one video demonstrating the fastest nystagmus SPV was used for reporting and analysis, unless otherwise noted. A minimum of three beats of nystagmus within a 15-s recording window was required for SPV analysis.

### Statistics

Statistical analysis was conducted with IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY: IBM Corp). Linear regression analyses were used to compare dependent variables including nystagmus SPV in °/s (ictal, interictal, spontaneous, and positional), lateral vHIT analysis [gain, saccade frequency (%), cumulative saccade amplitude (°), first saccade (S1) amplitude (°), peak velocity (°/s), onset (ms), and duration (ms)], and VEMP reflex symmetry (%), latency (ms), and amplitude (μV and CA). Comparisons were made between the VM and probable VM groups and age-matched normal controls. As the VEMP results were not normally distributed, a Kruskal–Wallis test was conducted to assess changes in test asymmetry in relation to disease duration. Descriptive statistics include means ± one standard deviation. Analyses were conducted within the framework of generalised estimating equations which accounts for the correlation in data when more than one observation per person is included. The output provided is the mean pairwise difference between conditions with a 95% confidence interval (CI), with a significance cut-off value of $p < 0.05$. Patient age was separated into 3 decade groups (< 40 years, 40–60 years, and > 60 years) and was included as a possible confounding independent variable in all of the above calculations [37].

## Results

### Patient characteristics

Over a period of four years, patients reporting recurrent spontaneous vertigo were convenience recruited (with informed consent) from an outpatient clinic. Patients were prospectively taught how to record nystagmus videos at home on a portable VOG device during episodes of vertigo. Patients who recorded eye videos during an attack of vertigo, and who had a final diagnosis of MD ($n = 55$), pMD ($n = 7$), and del-MD ($n = 8$) were included in the study. Patients with a high suspicion of autoimmune inner ear disease were excluded from the study ($n = 5$). Patients with a history of headache and/or migraine were included in the study ($n = 39$, 55.7%), and therefore, the possibility these patients are suffering from Vestibular Migraine concurrently cannot be excluded. Two patients had bilateral involvement, and the remaining had unilateral MD. The mean patient age at the time of assessment was 59 ± 14 years, including 33 males and 37 females. The mean duration of the disease before presenting for assessment to our clinic was 4.1 years (range 1 month–23 years). The mean age of disease onset was 55 years (range 27–84 years). No patients reported a family history of MD. The home VOG devices were loaned to patients for an average of 72 days, and patients recorded an average of 12 ictal videos (range 2–89). No adverse effects were reported by participants after using the home VOG device.

The most common presenting symptom was episodic spontaneous vertigo in 100% ($n = 70$) of patients; 98.6% ($n = 69$) reported true spinning vertigo, and 28.6% ($n = 20$) reported Mal de Débarquement. Clinical history and cardiovascular risk factors for patients with MD can be found in Table 1. The most common combination of labyrinthine symptoms was recurrent vertigo with tinnitus, aural fullness, and hearing loss (with or without fluctuations) in 53.1% ($n = 43$). The second most common combination of symptoms was recurrent vertigo with tinnitus in 27.1% ($n = 22$). Recurrent vertigo with hearing loss (with and without fluctuations) was reported in 17.3% ($n = 14$), and other combinations of symptoms in 2.5% ($n = 2$). Nausea and vomiting were reporting in 71.4% and 31.4%, respectively ($n = 50$ and 22). Other symptoms included disequilibrium/imbalance in 28.6% ($n = 20$), and motion sensitivity in 12.2% ($n = 10$). A further 55.7% ($n = 39$) reported headaches with associated visual aura in 11.4% ($n = 8$), photophobia in 7.1% ($n = 5$), and phonophobia in 2.9% ($n = 2$) (Table 1).

### Comorbidities

Five patients with MD also had a concurrent diagnosis of Benign Paroxysmal Positional Vertigo (BPPV), which was detected on bedside Dix–Hallpike testing, and treated with Epley manoeuvres. Two patients had posterior canal BPPV in the non-MD ear, two in the MD ear, and one patient with bilateral BPPV also had bilateral MD. Nystagmus observed during the BPPV treatment manoeuvres was not included in the study.

### Interventions

A low-salt diet was advised for all patients after diagnosis; 69.1% of patients ($n = 56$) were already on a salt-restricted

**Table 1** Clinical history and cardiovascular risk factors for 70 patients with MD

| Variable | MD ($n=55$) | pMD ($n=7$) | del-MD ($n=8$) | Total ($n=70$) |
|---|---|---|---|---|
| Gender, female, *n* (%) | 28 (50.9) | 3 (42.9) | 6 (75.0) | 37 (52.9) |
| Age, mean (SD) | 60.5 (13.8) | 47.6 (10.4) | 55.1 (12.9) | 58.6 (14.0) |
| Age at onset, mean years (SD) | 55.8 (14.9) | 45.2 (9.7) | 53.7 (12.7) | 54.5 (14.6) |
| Disease duration, mean years (SD)[†] | 4.7 (5.2) | 2.4 (2.6) | 1.4 (1.0) | 4.1 (4.8) |
| Headache/migraine, *n* (%) | 26 (47.3) | 7 (100.0) | 6 (75.0) | 39 (55.7) |
| Visual aura, *n* (%) | 7 (12.7) | 0 (0.0) | 1 (12.5) | 8 (11.4) |
| Photophobia, *n* (%) | 3 (5.5) | 2 (28.6) | 0 (0.0) | 5 (7.1) |
| Phonophobia, *n* (%) | 2 (3.6) | 0 (0.0) | 0 (0.0) | 2 (2.9) |
| Spinning vertigo, *n* (%) | 54 (98.2) | 7 (100.0) | 8 (100.0) | 69 (98.6) |
| Nausea, *n* (%) | 39 (70.9) | 6 (85.7) | 5 (62.5) | 50 (71.4) |
| Vomiting, *n* (%) | 18 (32.7) | 2 (28.6) | 2 (25.0) | 22 (31.4) |
| Disequilibrium/imbalance, *n* (%) | 15 (27.3) | 3 (42.9) | 2 (25.0) | 20 (28.6) |
| Mal de débarquement, *n* (%) | 16 (29.1) | 3 (42.9) | 1 (12.5) | 20 (28.6) |
| Motion sensitivity, *n* (%) | 7 (12.7) | 0 (0.0) | 1 (12.5) | 8 (11.4) |
| Tinnitus, unilat., *n* (%) | 46 (83.6) | 4 (57.1) | 5 (62.5) | 55 (78.6) |
| Tinnitus, bilat, *n* (%) | 0 (0.0) | 2 (28.6) | 0 (0.0) | 2 (2.9) |
| Subjective HL, unilat., *n* (%) | 44 (80.0) | 2 (28.6) | 7 (87.5) | 53 (75.7) |
| Subjective HL, bilat., *n* (%) | 2 (3.6) | 2 (28.6) | 0 (0.0) | 4 (5.7) |
| Aural fullness, unilat., *n* (%) | 35 (63.6) | 4 (57.1) | 1 (12.5) | 40 (57.1) |
| Aural fullness, bilat., *n* (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Hearing fluctuation, unilat., *n* (%) | 21 (38.2) | 2 (28.6) | 3 (37.5) | 26 (37.1) |
| Hearing fluctuation, bilat., *n* (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Diabetes type 2, *n* (%) | 7 (12.7) | 0 (0.0) | 0 (0.0) | 7 (10.0) |
| Dyslipidaemia, *n* (%) | 19 (34.5) | 4 (57.1) | 2 (25.0) | 25 (35.7) |
| Hypertension, *n* (%) | 19 (34.5) | 2 (28.6) | 2 (25.0) | 23 (32.9) |
| Ischaemic heart disease, *n* (%) | 2 (3.6) | 2 (28.6) | 0 (0.0) | 4 (5.7) |
| Current/ex-smoker, *n* (%) | 5 (9.1) | 0 (0.0) | 1 (12.5) | 6 (8.6) |
| VM differential diagnosis, *n* (%) | 8 (14.5) | 4 (57.1) | 3 (37.5) | 15 (21.4) |

Clinical features of definite, probable, and delayed Ménière's disease: [†]In delayed Ménière's disease cases, disease onset was determined from vertigo onset, not the onset of sudden hearing loss

*MD* Ménière's disease (definite), *pMD* probable Ménière's disease, *del-MD* delayed Ménière's disease, *SD* standard deviation, *bilat.* bilateral, *unilat.* unilateral, *VM* Vestibular Migraine

diet at the time of data collection. In most patients, preventative medications were in use at the time of testing: Betahistine in 82.7% ($n=67$), and a diuretic in 77.8% ($n=63$). Vestibular suppressants and antiemetics prescribed for use during acute episodes included prochlorperazine in 62.9% ($n=44$), ondansetron in 58.6% ($n=41$), and cinnarizine in 38.6% ($n=27$). Further interventions were undertaken in a subset of patients by their referring surgeons, and included intratympanic injection (ITI) of steroids in 22.9% ($n=16$), ITI gentamicin in 11.4% ($n=8$). Five patients underwent cochlear implantation, and three underwent labyrinthectomy. Home nystagmus event monitoring pre-dated the ablative procedures.

## Spontaneous nystagmus characteristics

Descriptive data for ictal nystagmus results are summarised in Table 2. All patients recorded videos during an episode of vertigo, and demonstrated spontaneous nystagmus in the upright position (gaze forward, without fixation), with a mean SPV of 42.8°/s (±31.1°/s, median 34.2°/s, range 5.3–160.1°/s) (Fig. 1). The main direction of the spontaneous nystagmus while upright was horizontal in 94.3% ($n=66$) (Online Resource 2), down-beating in 5.7% ($n=4$) (Online Resource 3), and up-beating in 1.4% ($n=1$). There was no significant difference in the spontaneous SPV of patients across the diagnostic sub-groups

**Table 2** Nystagmus in 70 patients with MD

| | Nystagmus slow-phase velocity (°/s) | | | | | |
|---|---|---|---|---|---|---|
| | Ictal | | | | Interictal | |
| | Primary | Supine | MD ear down | Non-MD ear down | Primary | Positional* |
| Mean | 42.8 | 27.1 | 33.4 | 24.3 | 1.4 | 2.4 |
| SD | 31.1 | 20.4 | 24.3 | 13.0 | 3.1 | 3.9 |
| Min | 5.3 | 0.0 | 7.5 | 0.0 | 0.0 | 0.0 |
| Q1 | 19.8 | 14.3 | 16.0 | 14.5 | 0.0 | 0.0 |
| Median | 34.2 | 22.8 | 26.9 | 22.4 | 0.0 | 0.0 |
| Q3 | 53.7 | 33.3 | 38.8 | 28.9 | 1.7 | 4.2 |
| Max | 160.1 | 88.3 | 95.2 | 56.0 | 16.8 | 24.6 |

Ictal and interictal spontaneous and positional nystagmus in Ménière's disease (without fixation): primary position in $n=70$, supine position in $n=24$, lying laterally with MD ear down in $n=18$, lying laterally with non-MD ear down in $n=20$. Interictal nystagmus was recorded in all ($n=70$) patients (all sub-groups combined).

*MD* Ménière's disease, *Max.* maximum, *Min.* minimum, *Q1* first quartile, *Q3* third quartile, *SD* standard deviation, *°/s* degrees per second

*Positional indicates nystagmus recorded in the supine, left- and right lateral lying positions or the Dix–Hallpike positions, combined

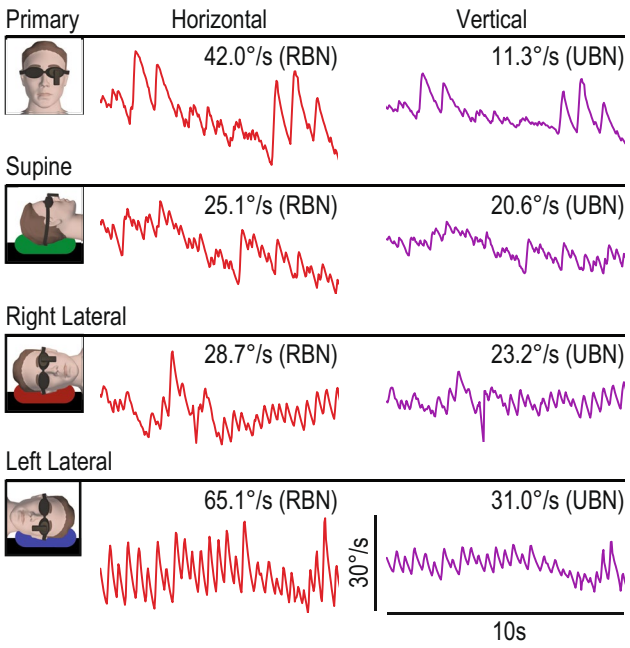


**Fig. 1** Upright and positional paretic phase nystagmus in a patient with definite Ménière's disease (MD) (left ear) showing right- and up-beating nystagmus which enhanced when lying laterally with the MD ear down. *RBN* right-beating nystagmus, *s* seconds, *UBN* up-beating nystagmus, *°/s* degrees per second

comparing MD, pMD and del-MD ($p=0.176$, 0.544 and 0.129). In all three MD sub-classifications combined, there was no significant difference in ictal spontaneous nystagmus SPVs between the age groups of < 40 years old, 40–60 years, and > 60 years ($p=0.346$, 0.580, and 0.523). In the two patients with bilateral MD, one demonstrated ictal spontaneous down-beating nystagmus (13.7°/s), as well as right-beating and left-beating nystagmus on different days, and the other patient showed right-beating nystagmus (34.1°/s) in the only video recorded.

## Positional nystagmus characteristics

Twenty-six patients with unilateral disease recorded ictal lying manoeuvres in conjunction with the upright position (Table 2). In the supine position, mean nystagmus SPV was 27.1°/s (± 20.4°/s, median 22.8°/s, range 0.0–88.3°/s). Lying laterally with the MD ear down, mean nystagmus SPV was 33.4°/s (± 24.3°/s, median 26.9°/s, range 7.5–95.2°/s). Lying laterally with the non-MD ear down, mean nystagmus SPV was 24.3°/s (± 13.0°/s, median 22.4°/s, range 0.0–56.0°/s). Compared with the ictal primary position nystagmus SPV (with gaze forward), there was no significant difference in nystagmus SPV when compared with the supine, MD ear down, or non-MD ear down lateral lying positions ($p=0.708$, 0.636, and 0.884). While some individual patients experienced an increase in nystagmus velocity lying laterally with the MD ear down (Fig. 1, Online Resource 4), there was no statistical significance between the MD ear down and non-MD ear down lying positions ($p=0.126$). However, there was a significant decrease in nystagmus velocity in the supine position as compared to the MD ear down position ($p=0.037$, CI 0.24–8.14).

## Direction-reversal nystagmus

All patients recorded more than one video, and 58.6% ($n=41$) of these captured a horizontal nystagmus direction reversal; 34.3% ($n=24$) demonstrated a direction reversal within the same episode of vertigo (recordings conducted within ≤ 12 h of each other, on the same day), and 24.3% ($n=17$) showed a direction reversal over different days, across different episodes of vertigo. The remainder of the patients ($n=29$) demonstrated unidirectional nystagmus in all recordings, with 62.1% ($n=18$) showing ipsilesional nystagmus (fast phase beating towards the affected ear), and 31.0% ($n=9$) showing contralesional nystagmus. The final two patients with bilateral disease demonstrated direction-fixed nystagmus (one right-beating, the other down-beating) in all videos.

There were 30 patients with multiple consecutive videos which recorded a nystagmus direction reversal within the same vertigo attack, including two patients who recorded two such attacks, all of whom had unilateral MD. Using the ear with the more significant hearing loss as a guide, 18.6% ($n=13$) captured an *irritative/paretic* direction reversal, 12.9% ($n=9$) recorded a *paretic/recovery* direction reversal, and 2.9% ($n=2$) recorded two back-to-back nystagmus direction reversals representing the full *irritative/paretic/recovery* nystagmus pattern (Fig. 2, Online Resource 5). Five patients recorded a single nystagmus direction reversal within the same video ([29]; Video 1C).

The spontaneous nystagmus SPVs of those with direction-reversing nystagmus within the same attack were plotted over time from the first video recording, assumed to be near the onset of vertigo (unless the patient verbally indicated otherwise on the audio recording). The mean *irritative/paretic* direction-reversal latency from first recording was 22.3 min, while the mean *paretic/recovery* nystagmus direction reversal was 51.1 min (Fig. 3). Both the mean raw nystagmus SPVs, and a percentage of the maximum SPV the patient displayed during a single attack, were plotted together. Combining both methods, the approximate interval between vertigo onset and the maximum nystagmus SPV fell between 135 and 165 min (2 ¼–2 ¾ h) from symptom onset.

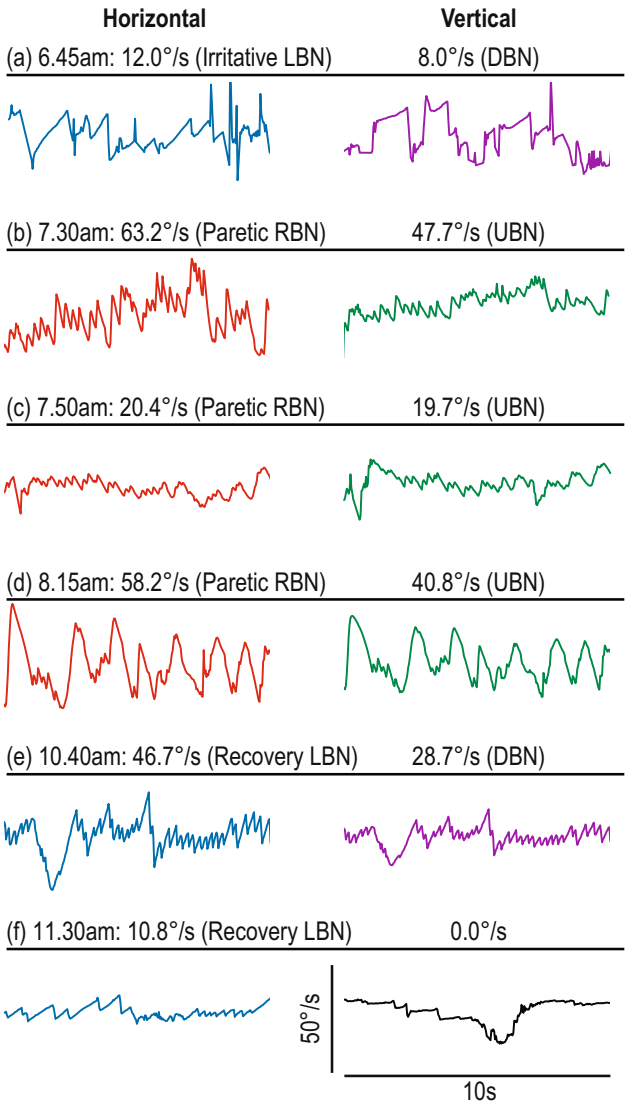


**Fig. 2** Nystagmus at the onset of a vertigo attack recorded in the upright position in a patient with definite MD (left ear), analysed in the horizontal and vertical planes. **a** is the first recording showing irritative, left- and down-beating nystagmus. **b–d** represent video recordings made over the next two hours showing a direction-reversal to right- and up-beating nystagmus. **e**, **f** represent the last two videos recorded which show a second direction reversal, and recovery left- and down-beating nystagmus. *DBN* down-beating nystagmus, *LBN* left-beating nystagmus, *RBN* right-beating nystagmus, *s* seconds, *UBN* up-beating nystagmus, *°/s* degrees per second

## Ictal vs interictal nystagmus

All patients either conducted interictal VOG with the primary investigator, or had interictal VOG (fixation denied) recorded in the process of conducting caloric testing (while supine before testing commenced), or during clinical examination (primary, supine, and Dix–Hallpike positions). In total, 22.9% of patients ($n=16$) displayed some degree of interictal spontaneous nystagmus, while 45.7% ($n=32$) had interictal positional nystagmus in at least one lying position. The mean interictal nystagmus in the primary position was 1.4°/s (± 3.1, range 0.0–16.8), while all lying positions combined showed a mean SPV of 2.4°/s (± 3.9, range 0.0–24.6) (Table 2). As compared with ictal spontaneous nystagmus, the ictal nystagmus SPVs were significantly faster ($p<0.001$, CI 34.28–48.78) (Fig. 4). Similarly, the positional nystagmus observed in the lying positions was significantly faster when ictal, as compared with interictal ($p<0.001$, CI 18.72–32.11).

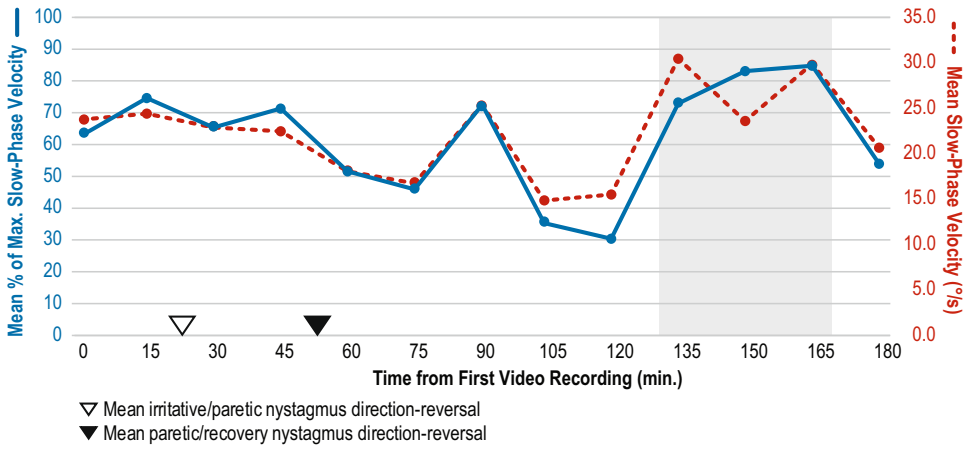


**Fig. 3** In 30 patients with multiple videos recorded at intervals during one attack of vertigo, mean nystagmus slow-phase velocity (dashed line), and a percentage of the maximum SPV recorded during that attack for each patient individually (solid line), are plotted together over time. The mean maximum nystagmus SPVs within a single attack occurred between 135 and 165 min from first recording, presumed to be at, or close to vertigo onset (grey area). The mean irritative/paretic direction-change latency from first recording was 22.3 min (white triangle), and the mean paretic/recovery nystagmus direction-change was 51.1 min (black triangle). *°/s* degrees per second, *max.* maximum, *min.* minutes

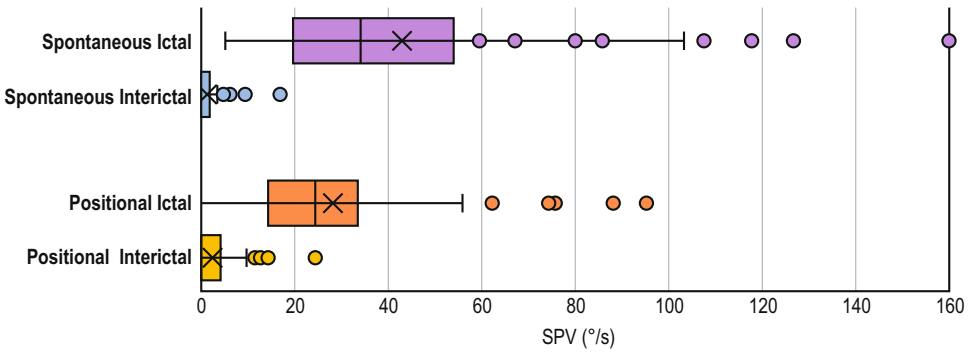


**Fig. 4** Ictal and interictal nystagmus slow-phase velocities (SPV) while sitting upright in the primary position, and in all lying positions combined. The interictal SPVs were significantly slower than the ictal, in both primary and positional recordings ($p < 0.001$, CI 34.277–48.776, $p < 0.001$, CI 18.716–32.113, respectively)

## Bithermal caloric test

In total, 57 patients received bithermal caloric testing with water irrigation. There was a significant unilateral canal paresis (> 25%) in 61.4% ($n = 35$) of patients, with the MD ear having reduced caloric responses as compared to the non-MD ear. The remaining 38.6% of patients ($n = 22$) showed normal symmetric responses. The mean canal paresis was 36 ± 24%. One patient with bilateral MD received caloric testing, and demonstrated a symmetric response.

## Video head impulse test (vHIT)

Lateral vHIT was conducted in 66 patients interictally and two patients showed VOR gains below normal limits; One patient had bilateral MD with the left lateral canal VOR reduction, the other patient had ipsilateral MD and canal reduction (neither patient had undergone ablative procedures). Compared with those of age-matched controls, lateral gains in MD ears were significantly lower, cumulative and first saccade (S1) amplitudes were significantly larger (°), and S1 peak velocities (°/s) were significantly faster ($p = 0.038$, 0.019, 0.008, and < 0.001, CI 0.01–0.07, 0.13–1.44, 0.14–0.91, and 14.61–41.51). However, there was no significant difference in total saccades (%) ($p = 0.108$), S1 onset (ms) ($p = 0.472$), or S1 duration ($p = 0.336$) when compared with controls (Table 3). Interestingly, in the non-MD ear in patients with unilateral MD, the lateral vHIT gains were significantly *larger* than controls ($p = 0.038$, CI 0.002–0.071). However, there was no significant difference in total saccades ($p = 0.535$), cumulative saccade amplitude ($p = 0.544$), S1 amplitude ($p = 0.609$), S1 peak velocity ($p = 0.069$), S1 onset ($p = 0.091$), or S1 duration ($p = 0.195$) in the non-MD ear as compared with controls [34, 38] (see Online Resource 6 for vHIT analysis diagram).

In total, 50 patients had both lateral vHIT and caloric testing. In this group, 60.0% ($n = 30$) had a significant

**Table 3** Audiovestibular test results

| | Mean (SD) | | | |
|---|---|---|---|---|
| Test | MD Ear | Non-MD Ear | VM | Control |
| AC cVEMP | (*n* = 54) | | (*n* = 81) | (*n* = 76) |
| P1 lat. (ms) | 11.8 (1.1) | 11.7 (0.9) | 11.7 (0.7) | 11.6 (0.7) |
| Corrected amp | 1.0 (0.7)* | 1.3 (0.6)* | 1.6 (0.7) | 1.8 (0.6) |
| Asymmetry ratio (%) | 40.3 (39.0)* | | 15.0 (16.9) | 11.3 (9.4) |
| AC oVEMP | (*n* = 36) | | (*n* = 54) | (*n* = 72) |
| N1 lat. (ms) | 8.7 (0.6) | 8.8 (0.7) | 8.7 (0.5) | 8.7 (0.6) |
| PP amp. (μV) | 7.4 (7.4) | 8.2 (7.6) | 9.2 (6.4) | 9.2 (6.5) |
| Asymmetry ratio (%) | 52.8 (40.2)* | | 28.3 (28.0) | 22.1 (21.9) |
| BC cVEMP | (*n* = 59) | | (*n* = 75) | (*n* = 75) |
| P1 lat. (ms) | 12.7 (0.8) | 13.1 (1.0) | 12.8 (1.0) | 12.9 (1.1) |
| Corrected amp | 1.3 (0.7)* | 1.5 (0.7)* | 1.6 (0.8)* | 2.0 (0.7) |
| Asymmetry ratio (%) | 20.4 (25.9) | | 11.9 (16.1) | 9.4 (7.4) |
| BC oVEMP | (*n* = 51) | | (*n* = 71) | (*n* = 75) |
| N1 lat. (ms) | 9.2 (0.4) | 9.2 (0.4) | 9.2 (0.5) | 9.1 (0.5) |
| PP amp. (μV) | 20.2 (11.3) | 21.6 (11.2) | 20.3 (12.8) | 19.8 (10.4) |
| Asymmetry ratio (%) | 12.8 (9.8) | | 13.3 (16.9) | 14.7 (12.1) |
| Lateral vHIT | (*n* = 50) | | (*n* = 58) | (*n* = 75) |
| Gain | 0.91 (0.2)* | 0.99 (0.1)* | 0.97 (0.1) | 0.95 (0.1) |
| Total saccades (%) | 81.2 (56.9) | 59.4 (36.6) | 51.1 (39.4) | 57.0 (31.2) |
| Cum. saccade amp. (°) | 1.6 (2.0)* | 0.9 (0.4) | 0.9 (0.6) | 0.8 (0.5) |
| S1 amp. (°) | 1.4 (1.2)* | 0.9 (0.4) | 0.9 (0.5) | 0.7 (0.4) |
| S1 peak velocity (°/s) | 98.0 (40.8)* | 79.0 (27.5) | 73.1 (30.1) | 62.6 (25.5) |
| S1 onset (ms) | 304.3 (90.3) | 336.8 (81.0) | 343.0 (74.9) | 316.5 (56.1) |
| S1 duration (ms) | 27.4 (8.3) | 25.2 (3.3) | 25.5 (5.0) | 25.9 (3.9) |
| Caloric | (*n* = 57) | | (*n* = 57) | (*n* = 0) |
| Canal paresis (%) | 35.9 (24.1) | | 16.4 (17.9) | – |
| DP (%) | 22.3 (17.2) | | 12.7 (13.1) | – |
| Electrocochleography | (*n* = 22 ears) | (*n* = 14 ears) | (*n* = 16 ears) | (*n* = 0) |
| Click SP/AP ratio (%) | 50.4 (19.6) | 23.6 (12.0) | 16.9 (11.0) | – |
| SP (μV) 0.5 kHz | − 6.2 (7.7) | − 0.9 (2.8) | 1.1 (1.9) | – |
| SP (μV) 1 kHz | − 7.3 (8.2) | − 0.4 (1.9) | 1.1 (1.7) | – |
| SP (μV) 2 kHz | − 9.9 (14.3) | − 1.3 (2.5) | 0.8 (1.6) | – |
| SP (μV) 8 kHz | 2.0 (2.7) | 0.2 (1.0) | 1.2 (0.8) | – |
| Audiometric threshold | (*n* = 70) | (*n* = 70) | (*n* = 76) | (*n* = 0) |
| Pure-tone average (dBHL) | 57.5 (22.8) | 25.2 (14.2) | 18.1 (13.3) | – |

Asterisks (*) represent values which are significantly different compared to those of normal controls. VEMP first peak latency, and peak-to-peak amplitude values for VM patients were calculated with right and left ear results combined. All ratios given in % were the mean and standard deviation of its absolute value. Audiometric threshold means include 0.25, 0.5, 1, 2, 4, 6 and 8 kHz to air-conducted stimuli

*AC* air conducted, *amp.* amplitude, *BC* bone conducted, *c* cervical, *CA* corrected amplitude, *Cum.* cumulative, *dBHL* decibels hearing level, *lat.* latency in milliseconds, *MD* Ménière's disease ear, *NC* normal controls, *N1* first negative peak, *o* ocular, *PP* peak-to-peak, *P1* first positive peak, *S1* first saccade, *SD* standard deviation, *SP/AP* summating potential versus action potential ratio, *VEMP* vestibular-evoked myogenic potential, ° degrees, *°/s* degrees per second

caloric CP and normal vHIT gains, 38.0% ($n = 19$) had normal results for both tests, 2.0% ($n = 1$) had both a reduced lateral vHIT gains and caloric CP, and none had a normal caloric with reduced vHIT. Thus, in MD patients who received both caloric and vHIT tests, 60.0% demonstrated a caloric/vHIT dissociation.

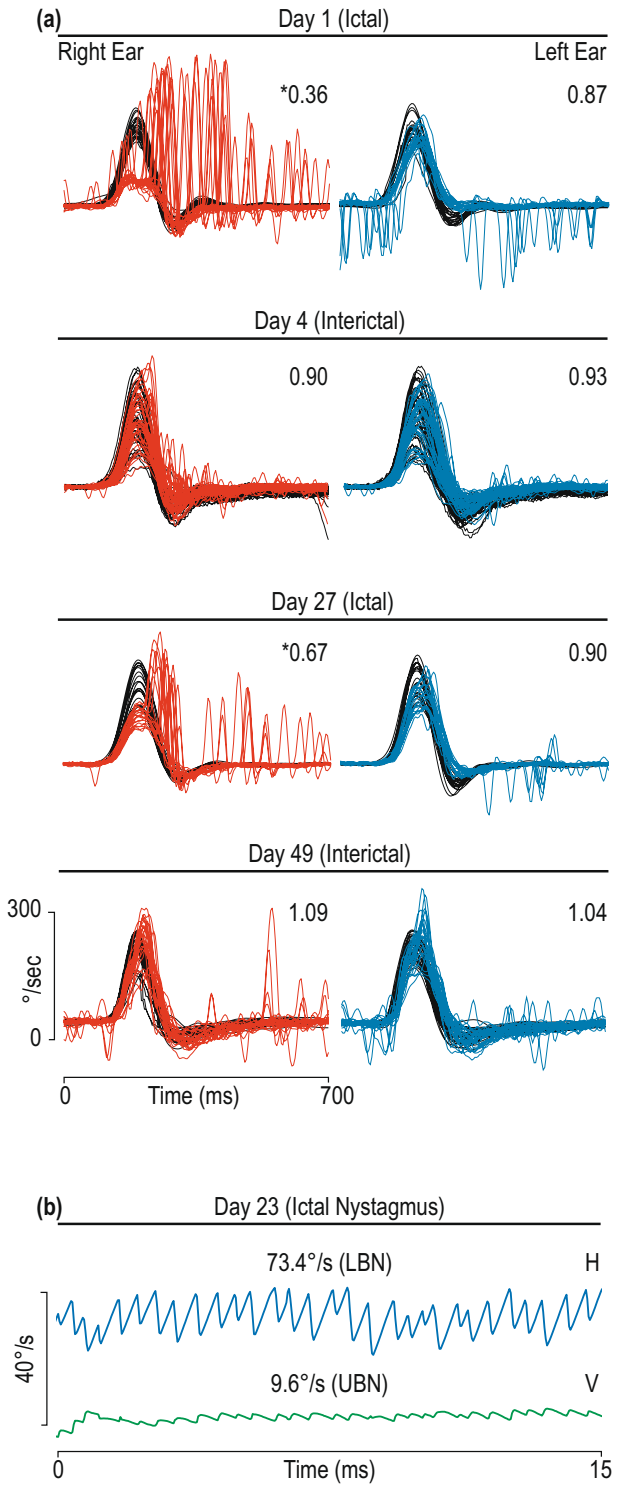


**Fig. 5** Over multiple outpatient visits, a patient with right Ménière's disease showed **a** fluctuating right lateral video head impulse test gains during the attacks of vertigo, which recovered interictally. The unaffected left ear shows normal gains throughout. A home video oculography recording (**b**) during an episode of vertigo captured primarily left-beating nystagmus, with a small up-beating component. *H* horizontal eye movements, *LBN* left-beating nystagmus, *ms* milliseconds, *UBN* up-beating nystagmus, *V* vertical eye movements, *°/s* degrees per second. Asterisks represent values which fall below those of normal controls

## Ictal video head impulse test

In two patients with unilateral MD, vHITs were undertaken during an acute attack. Patient 1 (right MD) attended the outpatient clinic on two separate occasions during an acute attack of vertigo, demonstrating high-velocity, left-beating paretic nystagmus (SPV 75.8°/s at first presentation), and a significantly reduced right lateral vHIT gain (0.36), with normal range gain (0.87) in the left (non-MD) ear. At clinical follow-up, the right lateral canal had shown significant improvement and a return to normal VOR gains (Fig. 5). Patient 2 (left MD) attended the outpatient clinic during an attack of MD and demonstrated reduced left lateral canal vHIT gains (0.61) with significant catch-up saccade frequency, right-beating paretic nystagmus (SPV 56.1°/s), and normal range gain (0.86) in the right (non-MD) ear. Eighteen days later the lateral vHIT gain had returned to normal (0.92) without significant catch-up saccade frequency.

## Audiometry

Pure-tone audiometry was conducted for all patients ($n=70$). At the patients' first audiometric assessment, 91.4% ($n=64$) displayed a hearing asymmetry at any frequency (MD ear with an increased threshold); of the two patients with bilateral disease, both showed bilateral low-frequency hearing loss: one had a symmetric flat moderately severe hearing loss, and the other had an asymmetry remaining in the low frequencies. After repeating audiometric testing in seven patients, a total of 100.0% ($n=70$) showed a hearing asymmetry. Using the most recent audiograms, 62.9% ($n=44$) showed an asymmetry which was flat (involving low, mid, and high frequencies), and 31.4% ($n=22$) showed a low-frequency asymmetry. In a sub-group of five patients, there was evidence of hearing asymmetry only in the high frequencies which later developed into a mid- and/or low-frequency hearing asymmetry. In another five patients, while there were hearing asymmetries at all frequency ranges, the high frequencies showed the greatest level of asymmetry, for reasons unknown (Fig. 6). A sub-group of four patients (5.7%) showed a high-frequency asymmetry only; three of these reported tinnitus and aural fullness, and had a significant caloric CP, while the fourth demonstrated a spontaneous horizontal nystagmus direction reversal and reported tinnitus. For these four patients, a diagnosis of pMD was given.

## Vestibular-evoked myogenic potentials (VEMP)

Descriptive data for VEMP results are summarised in Tables 3 and 4. Compared to the results of normal controls, AC and BC cVEMP reflexes in MD patients showed significant asymmetries between the ears in 37.3%, and 17.7% of patients. AC and BC oVEMP reflexes were significantly

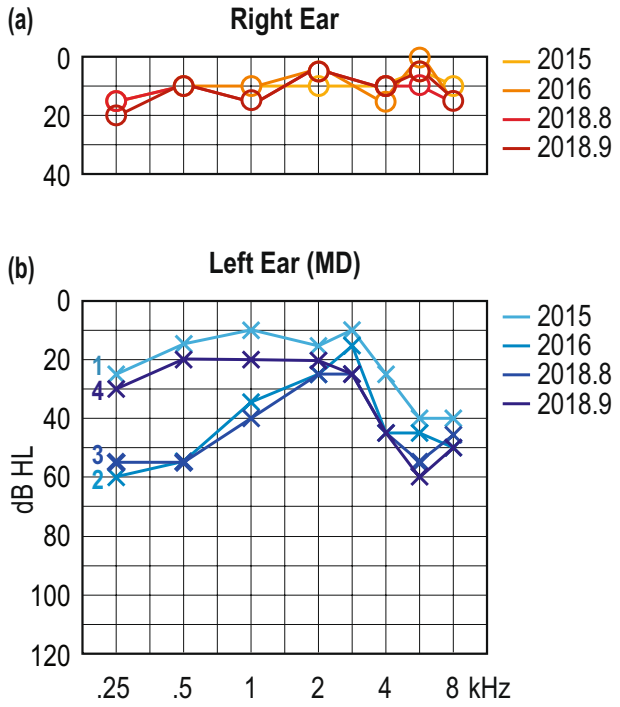


**Fig. 6** Audiograms recorded over three years in a 45-year-old female with definite left Ménière's disease (MD). The **a** right ear audiograms show normal and stable thresholds. The **b** left ear results show fluctuating low-frequency sensorineural hearing loss (tests 2 and 3), with alternating tests showing a greater loss and greater asymmetry in the high frequencies (tests 1 and 4). *db HL* decibels hearing level, *kHz* kilohertz, *2018.8* August, *2018.9* September

asymmetric (MD ear reduced) in 32.0%, and 1.8% of MD patients (Fig. 7). When comparisons were made between MD ears and those of normal controls, it was found that the MD ears showed significantly smaller AC and BC cVEMP-corrected reflexes amplitudes ($p < 0.001$, CI 0.33–0.81, and $p < 0.001$, CI 0.28–0.75). It was also found that the non-affected ear in patients with unilateral MD showed significantly smaller AC and BC cVEMP-corrected reflex amplitudes as compared with normal controls ($p = 0.017$, CI 0.05–0.48, and $p = 0.006$, CI 0.10–0.58).

Reflex amplitude asymmetry ratios (AR) of patients with MD (with MD ear being reduced) were significantly greater in both AC c- and oVEMP tests as compared with normal controls ($p = 0.001$, CI 8.88–36.60, and $p = 0.010$, CI 5.91–43.66). There were no significant differences in AR in either BC c- or oVEMP tests ($p = 0.083$ and $p = 0.407$) in patients with MD compared with normal controls. One patient with bilateral MD had cVEMPs conducted which showed 100% asymmetry ratio to AC stimuli, and normal symmetry to BC stimuli.

When patients with definite MD were categorised into three disease duration groups, A < 3 years, B 3–10 years and C > 10 years, the median (not normally distributed) AC cVEMP asymmetry ratios for the groups A, B and C were 16.0, 31.0, and 43.0%, respectively. The median AC oVEMP asymmetry ratios for the three groups were 34.9, 57.3 and 100.0%, respectively. A Kruskal–Wallis test showed a significant increase in AC cVEMP asymmetry ratios with disease length ($p = 0.018$). However, there was no significant correlation in disease duration and AC oVEMP asymmetry ratios ($p = 0.530$). Factors which may have affected the statistical significance for AC oVEMPs are that 36.1% of all patients had absent AC oVEMP reflexes bilaterally, and only five patients with disease duration > 10 years had AC oVEMP testing conducted.

## Electrocochleography (ECochG)

Transtympanic ECochG testing for the presence of endolymphatic hydrops (EH) was conducted for 22 MD patients, with 36 ears tested (22 MD ears, and 14 non-suspected MD ears). In total, 81.8% of the MD ears tested positive for EH. In the MD ears, the mean summating potential (SP) / action potential (AP) ratio for AC click stimuli was 50.4 (± 19.6) %, with mean SP to 0.5, 1, 2 and 8 kHz tone-bursts of − 6.2 (± 7.7), − 7.3 (± 8.2), − 9.9 (± 14.3), and 2.0 (± 2.7) µV. Of the 14 non-suspected MD ears tested, one showed a positive result for EH with an SP of − 7.1 at 2 kHz and an SP/AP ratio of 55%. Additionally, eight patients with a final diagnosis of Vestibular Migraine (who were excluded from this study), also had ECochG testing conducted due to reports of fluctuating unilateral aural symptoms ($n = 15$ ears tested). Using the same diagnostic criteria, only one ear of a VM patient had a positive result for EH, with an SP/AP ratio of 43% (with normal tone-burst SPs at all frequencies). The mean SP/AP ratio for the VM patients was 16.9%, with mean SP to 0.5, 1, 2 and 8 kHz tone-bursts of 1.1 (± 1.9), 1.1 (± 1.7), 0.8 (± 1.6), and 1.2 (± 0.8) µV. One patient with bilateral MD had ECochG testing on the ear with the most recent hearing loss (the other ear previously diagnosed as MD), with a positive result for the presence of EH.

## Separating Ménière's disease and Vestibular Migraine

We examined the efficacy of the audiovestibular test results in the differentiation of MD from Vestibular Migraine (VM). Data from 101 patients with VM and this cohort of 70 patients with MD were used [30]. Rates of abnormality (i.e. significant interaural asymmetry) for audiometry, caloric testing, VEMP, rates of reduced lateral vHIT gain, and vHIT/caloric dissociation are outlined in Fig. 8a.

Using nine metrics, we assigned a value for each parameter where '1' represented a value favouring a diagnosis of MD (a positive finding), and '0' represented a diagnosis of VM (a negative finding). The parameters used are as

**Table 4** Vestibular-evoked myogenic potential *p* values and confidence intervals in patients with Ménière's disease compared with normal controls

| | NC vs MD ears | | NC vs non-MD ears | | MD ears vs non-MD ears | |
|---|---|---|---|---|---|---|
| | *p* value | CI | *p* value | CI | *p* value | CI |
| AC Cvemp | | | | | | |
| P1 lat. | 0.730 | − 0.46 to − 0.32 | 0.603 | − 0.27–0.47 | 0.287 | − 0.14–0.47 |
| CA | < 0.001* | 0.33–0.81 | 0.017* | 0.05–0.48 | 0.002* | − 0.50 to − 0.11 |
| AR | 0.001* | 8.88–36.60 | | | | |
| AC oVEMP | | | | | | |
| N1 lat. | 0.115 | − 0.04–0.40 | 0.380 | − 0.14–0.37 | 0.302 | − 0.18–0.06 |
| Amp. | 0.898 | − 3.11–2.7 | 0.542 | − 4.17–2.19 | 0.485 | − 3.04–1.44 |
| AR | 0.010* | 5.91–43.66 | | | | |
| BC cVEMP | | | | | | |
| P1 lat. | 0.077 | − 0.04–0.67 | 0.688 | − 0.47–0.31 | 0.001* | 0.17–0.65 |
| CA | < 0.001* | 0.28–0.75 | 0.006* | 0.10–0.58 | 0.010* | 0.04–0.30 |
| AR | 0.083 | − 0.88–14.56 | | | | |
| BC oVEMP | | | | | | |
| N1 lat. | 0.126 | − 0.04–0.30 | 0.131 | − 0.04–0.29 | 0.896 | − 0.07–0.06 |
| Amp. | 0.223 | − 7.0–1.60 | 0.062 | − 8.21–0.20 | 0.193 | − 3.33–0.67 |
| AR | 0.407 | − 7.80–3.16 | | | | |

A total of 64 (out of 70) MD patients received at least one VEMP test. The number of patients tested in each category are as follows: AC cVEMP $n = 58$, BC cVEMP $n = 62$, BC oVEMP $n = 52$, AC oVEMP, $n = 36$. Asterisks (*) represent values which are significantly different to its compared metric. VEMP asymmetry ratios in those with MD were compared to those of normal controls ($n = 75$)

*AC* air conducted, *Amp.* amplitude in μV, *BC* bone conducted, *c* cervical, *CA* corrected amplitude, *lat.* latency in milliseconds, *MD* Ménière's disease, *N1* first negative peak, *o* ocular, *P1* first positive peak, *VEMP* vestibular-evoked myogenic potential

follows; (1) spontaneous recurrent vertigo, (2) ≥ 1 unilateral fluctuating aural symptom, (3) audiogram asymmetry at low- and/or mid frequencies, (4) ictal horizontal nystagmus SPV > 12°/s, (5) caloric CP > 25%, (6) caloric/vHIT dissociation, (7) AC cVEMP asymmetry ratio > 30%, (8) AC oVEMP asymmetry ratio > 39.9%, and (9) lateral vHIT gain < 0.72 [34]. The sensitivity and specificity for each test individually in a correct diagnosis of MD are listed in Table 5, and the sensitivity and specificity for composite scores of these test results is shown in Fig. 8b. The three metrics with the most favourable sensitivity and specificity in isolation are (1) audiogram asymmetries, (2) spontaneous horizontal nystagmus with SPV > 12°/s, and (3) unilateral fluctuating aural symptoms, with sensitivities and specificities of 94.3/97.0%, 91.4/92.1%, and 95.7/73.3% respectively (CIs 0.92–0.99, 0.87–0.97, 0.79–0.91, respectively). After audiogram threshold asymmetries, the two objective tests with the highest diagnostic yield were the ictal nystagmography and interictal caloric test, and when combined yielded a sensitivity and specificity of 95.7% and 85.1% (CI 0.87–0.97) for a positive diagnosis of MD (Table 6). However, as most clinics do not have the ability to measure ictal nystagmus for every MD patient at this time, a calculation was made using just the caloric test results and cVEMP results (as both tests are commonly available in neurology or audiology clinics); here, MD was correctly diagnosed with a sensitivity and specificity of 67.1% and 88.1% (CI 0.71–0.86).

We also examined the utility of Machine Learning techniques in separating VM and MD by applying a linear support vector machine classifier to the metrics itemised in Table 5, excluding asymmetric hearing loss and unilateral fluctuating aural symptoms. Using these variables, MD was diagnosed with 91.8% accuracy, with 91.4% sensitivity and 92.1% specificity [39]. Individual patient test results and symptom scores are listed in Online Resources 7–8.

## Discussion

In the present study, we examined clinical, oculographic and audiovestibular test characteristics of MD. MD was associated with high-velocity horizontal spontaneous nystagmus which demonstrated direction reversal, significant caloric CP, and normal interictal vHIT gains. Greater cVEMP asymmetry ratios and lower reflex amplitudes were found in MD ears as compared with normal controls, also found by other investigators [33]. Ictal nystagmography with interictal caloric test results gave a sensitivity and specificity of 95.7% and 85.1% for a positive diagnosis of MD, whereas a caloric test with cVEMP results correctly diagnosed MD with a sensitivity and specificity of 67.1% and 88.1%.

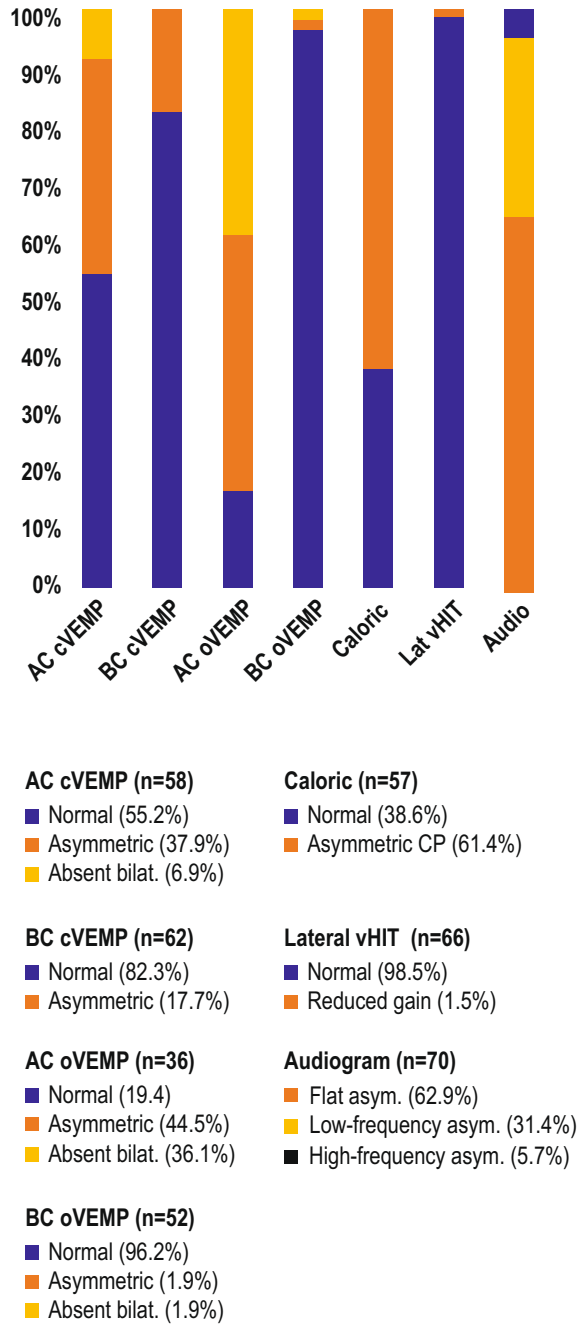


**Fig. 7** Audiovestibular test results in $n=70$ patients with Ménière's disease. *AC* air conducted, *asym.* asymmetry, *BC* bone conducted, *bilat.* bilaterally, *c* cervical, *CP* canal paresis > 25%, *lat.* lateral canal, *o* ocular, *vHIT* video head impulse test

## Should vestibular tests be considered in the diagnostic criteria for MD?

The benefits of including audiovestibular test results in the diagnostic criteria for MD are that objective test measures combined with the patient history may facilitate earlier diagnosis. Increasing the number of diagnostic indicators in each patient may lead to inclusion of early MD patients with normal audiometry. The drawbacks of including audiovestibular test results include the lack of internationally standardised vestibular test protocols. For example, clinics conducting caloric tests may use different stimuli (water or air), stimulus durations, and protocols. Also, while the AC cVEMP test of symmetry is relatively high in diagnostic yield, asymmetry rates differ greatly based on stimulus sound level, waveform (500 Hz tone-burst vs click), and normative cut-off values.

## Which vestibular tests should be included in the diagnosis of MD?

In our study, the test which yielded the highest rate of abnormality was pure-tone audiometry, with 100.0% of MD patients showing a significant asymmetry (unilateral increased threshold) at any frequency range. This was followed by 61.4% with significant caloric CP, caloric–vHIT dissociation in 60%, and significant AC oVEMP and cVEMP asymmetry in 44.4% and 37.9%. Based on our observations, audiogram asymmetry at low- and/or mid frequencies, enables diagnosis of MD with highest sensitivity and specificity, and often no further testing is required. When we examined the utility of vestibular tests alone in the context of spontaneous vertigo, the video nystagmography, caloric test, caloric–vHIT dissociation and VEMP asymmetry assisted with diagnosis of MD.

Furthermore, ictal nystagmography alone may help to separate VM from MD. As roughly half (55.7%) of the patients in this study reported a significant headache and/or migraine history, it is likely that at least a portion of the MD group may have a concurrent diagnosis of Vestibular Migraine. As it is known VM may also manifest with rotatory vertigo and nystagmus [40], it is plausible these patients with both diseases may have a different nystagmus profile. However, in this MD group, statistical analysis showed no correlation between ictal nystagmus slow-phase velocity and migraine/headache history ($p=0.270$). Coupled with the significant difference found in nystagmus SPV between purely VM and all MD sufferers, it appears having a diagnosis MD causes a significant nystagmus velocity enhancement even in patients with both diseases, further helping to confirm a diagnosis of MD in those patients with a history of both headache and vertigo.

## Comparison with previous studies

The high prevalence of reduced cVEMP reflexes (thought to represent the saccular pathway), and hearing asymmetries, is corroborated by other early MD studies showing that endolymphatic hydrops is most often found in the pars inferior, affecting the cochlea and saccule [12, 41–43]. Our findings are similar to those of earlier investigators which

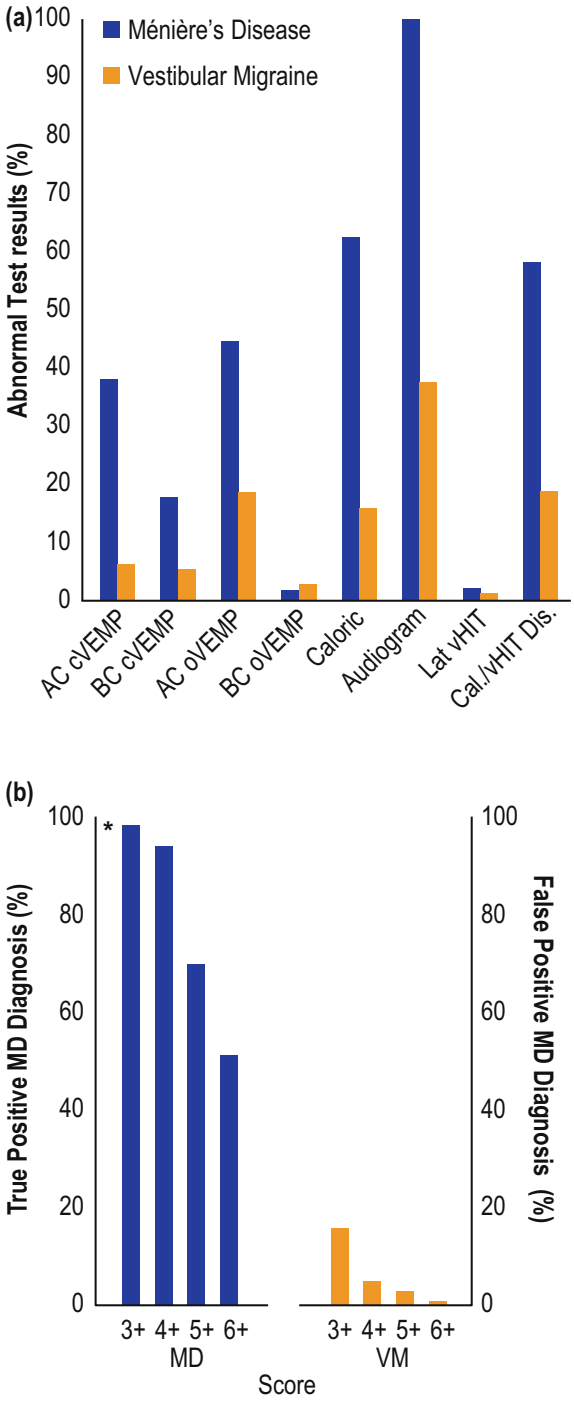


**Fig. 8** **a** Audiovestibular test abnormalities include significant asymmetry ratios for VEMPs, caloric tests > 25% canal paresis, audiograms which had a significant asymmetry at any frequency range, and caloric/vHIT dissociation (i.e. caloric canal paresis and age-normal lateral vHIT gain). *AC* air conducted, *BC* bone conducted, *c* cervical, *Dis.* dissociation, *o* ocular, *VEMP* vestibular-evoked myogenic potential, *vHIT* video head impulse test. **b** Using nine metrics, we assigned a value for each parameter where '1' represented a value favouring a diagnosis of Ménière's disease (a positive finding), and '0' represented a diagnosis of VM (a negative finding). The parameters used are as follows; (1) audiogram asymmetry at low and/or mid frequencies, (2) caloric canal paresis > 25%, (3) air conducted (AC) cervical vestibular-evoked myogenic potential (VEMP) asymmetry ratio > 30%, (4) AC ocular VEMP asymmetry ratio > 39.9%, (5) lateral video head impulse test (vHIT) gain < 0.72, (6) ictal horizontal nystagmus slow-phase velocity > 12.1°/s, (7) caloric/vHIT dissociation, (8) ≥ 1 unilateral fluctuating aural symptom, and (9) episodic spontaneous vertigo. A score > 3 correctly diagnosed MD with a sensitivity and specificity of 95.7% and 95.0%, shown with asterisk (CI 0.95–0.10)

reported an interaural cVEMP reflex amplitude asymmetry (33%–82%) which is significantly more common in those with MD (MD ear being reduced) as compared with normal controls, and a high rate of abnormality in caloric testing (28–75%) [15, 27, 33, 44–47]. It has been found that testing at different stages of the disease results in different levels of abnormality, generally increasing with disease progression, which may explain the wide range of test results in the literature [26, 27, 47]. The audiogram is a mainstay of an audiology clinic, fast and non-invasive, and should be at the forefront of diagnostic testing in any patient with recurrent spontaneous vertigo. Like our results, other studies have shown sequential audiograms in patients with MD where at least one test shows asymmetry in the high frequencies, before evolving into low- and mid-frequency asymmetries [23].

## Caloric/vHIT dissociation

Many investigators have highlighted the puzzling finding of normal lateral vHIT gains with significant lateral canal paresis with caloric testing in patients with MD [15, 16, 48, 49]. The hypothesis put forward is that bulging within the lateral canal duct cause by excessive endolymphatic fluid allows the warm or cool water caloric irrigation to produce a small localised convention flow within the duct but avoids deflecting the cupula, resulting in no nystagmus and an apparent loss of function in that ear, whereas this fluid has no dampening effect on rotational stimulation during a lateral head impulse [16]. The caloric/vHIT dissociation rate in our study was 60%, making it more sensitive than lateral vHIT gain results, but less sensitive than caloric test values on their own. The video head impulse test is now widely available in vestibular testing facilities worldwide.

## Availability of equipment for ictal assessment

The nystagmus event-monitors used in our study were custom made and not commercially available for widespread use. Current models of portable iPad audiometry kits are becoming more widely available, and should be used at home by patients in cases of reported hearing fluctuations which have eluded clinical detection [50, 51].

**Table 5** Audiovestibular test results and presenting symptoms of 70 MD patients and 101 VM patients

| Audiovestibular result | MD (%) | VM (%) | Sensitivity for MD (%) | Specificity for MD (%) | 95% CI |
|---|---|---|---|---|---|
| Episodic spontaneous vertigo | 100.0 | 93.1 | 100.0 | 6.9 | 0.45–0.62 |
| Unilat. fluct. aural symptoms | 95.7 | 26.7 | 95.7 | 73.3 | 0.79–0.91 |
| Audiogram. asym. | 94.3 | 3.0 | 94.3 | 97.0 | 0.92–0.99 |
| Ictal spont. horiz. nyst. > 12.1°/s | 91.4 | 7.9 | 91.4 | 92.1 | 0.87–0.97 |
| Caloric CP > 25.0% | 52.9 | 8.9 | 52.9 | 91.1 | 0.64–0.80 |
| Caloric/vHIT dissociation | 41.4 | 8.9 | 41.4 | 91.1 | 0.58–0.75 |
| AC cVEMP asym. > 30.0% | 31.4 | 5.0 | 31.4 | 95.0 | 0.55–0.72 |
| AC oVEMP asym. > 39.9% | 24.3 | 10.9 | 24.3 | 89.1 | 0.49–0.66 |
| Lat vHIT < 0.72 in at least one ear | 2.9 | 1.0 | 2.9 | 99.0 | 0.42–0.60 |

The percentage of patients with a positive result in each of the nine categories are listed, as well as the sensitivity and specificity for a correct diagnosis of MD for each test individually. The three metrics with the most favourable sensitivity and specificity combinations for a diagnosis of MD are highlighted in grey (unilateral fluctuating aural symptoms, audiogram asymmetries, and spontaneous horizontal nystagmus with SPV > 12.1°/s, and). Audiogram asymmetries represent the MD ear having the higher threshold in the low–mid-frequencies

*Asym.* asymmetry, *AC* air conducted, *BC* bone conducted, *c* cervical, *fluct.* fluctuating, *Horiz.* Horizontal, *CI* confidence interval, *CP* canal paresis, *Lat.* lateral canal, *MD* Ménière's disease, *nyst.* nystagmus, *o* ocular, *Spont.* spontaneous, *Unilat.* unilateral, *VEMP* vestibular-evoked myogenic potential, *vHIT* video head impulse test

## Pathophysiology of direction-reversal nystagmus

In the fluid '*drainage theory*' of MD, a physiological 'valve' would be periodically forced open to release the excessive endolymphatic fluid away from the saccule and cochlea and into the adjacent areas encompassing the utricle and semicircular canals [9, 11, 12, 41]. In this way, deviation of the lateral semicircular cupula towards the ampulla would excite its afferents and produce ipsiversive nystagmus (likely the first *irritative* phase of nystagmus), and when the excessive fluid drains away sufficiently, the cupula is thought to deviate in the opposite direction, inhibiting its afferents and causing contraversive nystagmus [8]. The tipping point of the endolymphatic fluid build-up and its sudden release likely constitute the ictal period of the MD attack, followed by recovery nystagmus, switching back to its ipsiversive fast phase whilst slowing in velocity. This final phase likely represents mechanisms of central adaptation after a period of prolonged unilateral stimulation of the vestibular system [4, 6–8]. If there has been some central adaptation, a return back to the resting discharge of the MD ear may be interpreted as a stimulus in the opposite direction by the CNS, relative to the original asymmetry in function [52]. Previous investigators reported the first irritative, or ipsiversive nystagmus early in an attack of MD, usually only lasting minutes [4, 6–8, 23, 53].

## Study limitations

We were unable to provide definitive timing from vertigo onset in the group, and relied on self-reporting methods; Patients were counselled to verbally indicate the time from vertigo onset in the home video recordings, and while most patients were able to impart this information, a subset were unable or had forgotten. The inclusion of *probable*, *delayed,* and *definite* cases of MD may influence the diagnostic accuracy of nystagmus SPV measurement, as some cases may evolve over time. Although the diagnostic classification of patients was conferred by clinical means of case history and audiovestibular test results, the investigators were not blinded to the ictal nystagmus VOG recordings, which may have influenced the diagnostic process. Antiemetic and vestibular suppressant medications taken at symptom onset (including prochlorperazine, cinnarizine and/or ondansetron) may have unknown effects on nystagmus slow-phase velocities. As patients with a history of headache and/or migraine were included in the study, there is a likelihood some patients have a comorbid diagnosis of Vestibular Migraine, which may have influenced test results. Lastly, as the participants were convenience recruited, a sampling bias cannot be excluded due to voluntary participation, and as this study was conducted from a single centre, results may not be generalisable to a wider population.

## Conclusion

Diagnosing the aetiology of episodic spontaneous vertigo is an important undertaking which is likely to offer symptom relief to many vertigo sufferers. Our observations indicate that audiometry, vHIT, VEMP, caloric test, and ictal nystagmus event monitoring combined may provide

**Table 6** The following five most common audiovestibular test abnormalities in patients with Ménière's disease (MD) have been compared to those with a diagnosis of Vestibular Migraine, and given a sensitivity and specificity for each possible score when added sequentially in order of prevalence in patients with MD

| | Sensitivity for MD (%) | Specificity for MD (%) | 95% CI |
|---|---|---|---|
| For test 1 | | | 0.87–0.97 |
| A score of 1/1 | 91.4 | 92.1 | |
| For tests 1 + 2 | | | 0.89–0.97 |
| A score of 2/2 | 48.6 | 98.0 | |
| For a score of 1/2 | 95.7 | 85.1 | |
| For tests 1 + 2 + 3 | | | 0.87–0.96 |
| A score of 3/3 | 37.1 | 98.0 | |
| A score of 2/3 | 52.9 | 91.1 | |
| A score of 1/3 | 95.7 | 85.1 | |
| For tests 1 + 2 + 3 + 4 | | | 0.87–0.96 |
| A score of 4/4 | 7.1 | 99.0 | |
| A score of 3/4 | 47.1 | 97.0 | |
| A score of 2/4 | 67.1 | 90.1 | |
| A score of 1/4 | 95.7 | 83.2 | |
| For tests 1 + 2 + 3 + 4 + 5 | | | 0.87–0.96 |
| A score of 5/5 | 5.7 | 99.0 | |
| A score of 4/5 | 15.7 | 98.0 | |
| A score of 3/5 | 52.9 | 97.0 | |
| A score of 2/5 | 70.0 | 89.1 | |
| A score of 1/5 | 97.1 | 75.2 | |

Tests include: (1) Ictal spontaneous horizontal nystagmus > 12.1°/s, (2) caloric canal paresis > 25%, (3) caloric/video head impulse test dissociation, (4) air-conducted (AC) cervical vestibular-evoked myogenic potential (VEMP) test asymmetry > 30%, (5) AC ocular VEMP asymmetry > 39.9%

*CI* confidence interval

better diagnostic separation than each test in isolation. The development of globally standardised vestibular test parameters and a case history questionnaire should be a goal of the neuro-otology and audiology specialties, in the hope increasing the yield and accuracy of diagnostic criteria for Ménière's disease.

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**Data availability** Anonymised data may be shared with investigators, upon request, in the context of research collaboration.

**Code availability** Custom nystagmus analysis software may be shared with interested parties.

## Declarations

**Conflicts of interest** A Young receives scholarship funding from the University of Sydney, and funding from the Garnett Passe and Rodney Williams Memorial Foundation, and reports no conflict of interest. J Pogson receives funding from the Garnett Passe and Rodney Williams Memorial Foundation and reports no conflict of interest. M Welgampola receives funding from the Garnett Passe and Rodney Williams Memorial Foundation, and the National Health and Medical Research Council of Australia, and reports no conflict of interest. B Nham, A Bradshaw, Z Calic, W Gibson, and G Michael Halmagyi report no conflicts of interest.

**Ethical approval** This study received local ethics committee approval (Protocol No X18-0087). Written informed consent was obtained from all participants in accordance with the 1964 Declaration of Helsinki and its later amendments.

**Consent to participate** Not applicable.

**Consent for publication** Not applicable.

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