Auditory and Vestibular Symptoms and Chronic Subjective Dizziness in Patients With Ménière's Disease, Vestibular Migraine, and Ménière's Disease With Concomitant Vestibular Migraine

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Objective: To compare presentations of Ménière's disease (MD), vestibular migraine (VM), and Ménière's disease plus vestibular migraine (MDVM), with and without comorbid chronic subjective dizziness (CSD).

Study Design: Retrospective review with diagnosis confirmed by consensus conference of investigators using published criteria for MD, VM, and CSD.

Setting: Ambulatory, tertiary dizziness clinic.

Patients: Approximately 147 consecutive patients with diagnoses of MD, VM, or MDVM, with/without comorbid CSD.

Interventions: Diagnostic consultation.

Main Outcome Measures: Similarities and differences between diagnostic groups in demographics; symptoms; and results of neurotologic, audiometric, and vestibular laboratory assessments. Results: Seventy-six patients had MD, 55 MD alone. Ninety-two patients had VM, 71 VM alone. Twenty-one patients had MDVM, representing about one-quarter of those diagnosed with MD or VM. Clinical features thought to differentiate VM from MD were

found in all groups. Twenty-seven patients with VM (38%) had ear complaints (subjective hearing loss, aural pressure, and tinnitus) during episodes of vestibular symptoms and headache, including 10 (37%) with unilateral symptoms. Conversely, 27 patients with MD alone (49%) had headaches with migraine features that did not meet full IHS diagnostic criteria, migrainous symptoms (photophobia, headache with vomiting), or first-degree relative with migraine. Including MDVM patients, 59% (45/76) of all patients with MD had migrainous features. Thirty-two patients had CSD; most (29; 91%) were in the VM group.

Conclusion: Comorbidity was common between MD and VM, and their symptoms overlapped. More specific diagnostic criteria are needed to differentiate these diseases and address their coexistence. CSD co-occurred with VM but was rarely seen with MD. Key Words: Chronic subjective dizziness—Dizziness—Ménière's disease—Migraine—Sensorineural hearing loss—Vertigo—Vestibular migraine.

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The classic presentation of episodic vertigo, tinnitus, and hearing loss is considered by many experts to be indicative of Ménière's disease (MD) (1). However, patients who have variations of this presentation and those who

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experience persistent unsteadiness or dizziness between vertigo attacks present difficult diagnostic challenges. Two recently defined conditions may shed light on this problem, if their relationship to MD can be elucidated. Vestibular migraine (VM), first defined by Neuhauser et al. (2) in 2001, is a condition of episodic vertigo linked to migraine headache. Its acute vestibular symptoms are frequently indistinguishable from those of MD. Numerous authors, including Prosper Ménière, commented on the coexistence of MD and migraine (3). Chronic subjective dizziness (CSD), described by Staab et al. (4) in 2004, is a syndrome of persistent unsteadiness and nonvertiginous dizziness that is increasingly recognized as a frequent sequela of episodic vestibular conditions. Unsteadiness and dizziness that persist after acute vertigo attacks are

frequently thought to be due to incompletely compensated vestibular deficits, but recent prospective studies point to CSD as a much more common cause (5,6). Thus, patients who experience recurrent vertigo episodes may have more than 1 condition (i.e., MD, VM, or both), and those who have persistent unsteadiness or dizziness after acute vestibular crises may have CSD, not an uncompensated vestibular deficit.

Ménière's Disease

The incidence of MD has been estimated at 0.2% of the population (600,000 US citizens) (7). Limited progress has been made toward establishing the underlying pathophysiology and firmly outlining the diagnostic parameters and treatment approaches for these patients. Endolymphatic hydrops (EH) has long been touted as the underlying pathology of MD. However, more recent evidence has questioned this dogma and suggests that EH may be an epiphenomenon to an unknown inner ear etiology (1,8). To date, genetic studies have not identified a causative gene (9,10). The most recent clinical criteria were developed in 1995 by the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) (11) (Table 1). These criteria fundamentally rely on patient history and audiogram. Publications have provided interesting yet unproven hypotheses concerning possible disease relationships or mechanisms including the following: autoimmunity, allergy, trauma, and environmental causes. There is strong clinical evidence that migraine and MD are comorbid in a large number of patients. A prospective, controlled epidemiology study showed a higher incidence of migraine headache in MD patients

TABLE 1. 1995 committee on hearing and equilibrium guidelines for Ménière's disease diagnosis

Certain Ménière's disease

Definite Ménière's disease, plus histopathologic confirmation. Definite Ménière's disease

Two or more definitive spontaneous episodes of vertigo 20 minutes

Audiometrically documented hearing loss on at least one occasion. Tinnitus or aural fullness in the treated ear.

Other causes excluded.

Probable Ménière's disease

One definitive episode of vertigo.

Audiometrically documented hearing loss on at least one occasion. Tinnitus or aural fullness in the treated ear.

Other causes excluded.

Possible Ménière's disease

Episodic vertigo of the Ménière's type without documented hearing loss, or

Sensorineural hearing loss, fluctuating or fixed, with disequilibrium but without definitive episodes.

Other causes excluded.

Audiometrically documented hearing loss is defined as the following: 1) the average hearing threshold at 0.25, 0.5, and 1 kHz is 15 dB or greater worse than the average of 1, 2, and 3 kHz; 2) in unilateral cases, the PTA (0.5, 1, 2, and 3 kHz) is 20 dB or greater worse in the suspected ear than the opposite side; and 3) in bilateral cases, the PTA (0.5, 1, 2, and 3 kHz) is 25 dB or greater in both ears.

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TABLE 2. Diagnostic criteria for vestibular migraine or migrainous vertigo (2,19)

Definite vestibular migraine (need to meet A-D)

- Episodic vestibular symptoms of at least moderate severity.
- B. Current or previous history of migraine according to the 2004 ICHD-II criteria.
- C. One of the following migraine symptoms during 2 or more vertigo attacks: migrainous headache, photophobia, phonophobia, visual aura, or other aura (dizziness not included).
- D. Other causes ruled out by appropriate investigations.

Note: vestibular symptoms are defined as rotational vertigo or another illusory self motion or object-motion. Moderate severity- symptoms interfere but do not prohibit daily activities.

Probable vestibular migraine (need to meet A-C)

- A. Episodic vestibular symptoms of at least moderate severity.
- B. One of the following:
 - (1) Current or previous history of migraine according to the 2004 ICHD-II criteria;
 - (2) Migrainous symptoms of photophobia, phonophobia, aura, or other aura during vestibular symptoms;
 - (3) Migraine precipitants of vertigo in more than 50% of vertigo attacks: food triggers, sleep irregularities, or hormonal changes;
- (4) Response to migraine medications in more than 50% of attacks.

C. Other causes ruled out by appropriate investigations.

ICHD-II indicates International Classification of Headache Disorders, 2nd edition, by the International Headache Society (37).

compared with the general population. Conversely, MD is more prevalent in a migraine headache population (12–14).

Vestibular Migraine

Although the incidence of migraine in the general population is 15% to 17% in women and 6% in men, the prevalence of VM has been estimated at 1% to 3% of the population (3–9 million US citizens) (7,15–18). Diagnostic criteria for VM were updated by Neuhauser and Lempert (19) in 2009 (Table 2). Patients with VM may experience spontaneous episodes of vertigo lasting from seconds to days. Hours-long attacks can mimic MD, and short attacks may have positional elements that imitate benign paroxysmal positional vertigo. VM patients also commonly report head motion intolerance, motion sickness, episodes of vertigo provoked by head movements, nausea, and imbalance. Vertigo and headaches may occur together or, more controversially, have no temporal relationship (20–23). Transient fluctuating hearing loss, aural fullness and tinnitus, and audiometrically documented mild sensorineural hearing losses (SNHLs) also have been described in VM (14,24). This makes differentiating VM from early MD extremely difficult, with attention focused on judgments about how much SNHL is too much to be considered VM

Several pathophysiologic links have been proposed between MD and VM, including shared genetic susceptibility (25), common underlying channelopathy (26–28), dual effects of neurotransmitters (serotonin, norepinephrine, and glutamate) or neuropeptides (calcitonin gene-related peptide) on vestibular and trigeminal neurons (21,29), and a sequential hypothesis in which migraine-induced microvascular ischemic damage to the inner ear is posited to lead to a MD-like presentation (12,30).

Chronic Subjective Dizziness

CSD is a condition of chronic unsteadiness or nonvertiginous dizziness accompanied by hypersensitivity to motion stimuli and poor tolerance for complex visual stimuli or precision visual tasks that lasts for 3 months or more (Table 3) (31,32). The definition of CSD was refined from the earlier concept of phobic postural vertigo (33). Originally, CSD was identified in patients who had no evidence of active neurotologic illnesses. However, clinical experience over the last decade and emerging diagnostic studies indicate that it can coexist with recurrent vertiginous syndromes such as MD and VM. A careful history of persistent dizziness and motion sensitivity in the interictal period between the spontaneous vertigo bouts is the cornerstone to making the diagnosis of concomitant CSD. The cause of CSD is not understood, but there is evidence to suggest that, like migraine, central nervous system serotonergic pathways may be involved (4).

The primary goals of this study were to examine comorbidity and overlapping diagnostic features among MD, VM, and CSD and identify clinical variables that would best separate these conditions, thereby improving diagnostic accuracy and treatment outcomes. Similarities and differences in clinical variables also might provide insight into pathophysiologic mechanisms.

MATERIALS AND METHODS

Study Design and Patient Selection

Subjects were collected from a retrospective medical record review of 600 consecutive patients (2008–2009) with the chief complaint of vertigo, unsteadiness, or dizziness evaluated at a tertiary referral dizziness clinic. Of these, 147 patients with consensus diagnoses of MD, VM, or both (MDVM), with or without comorbid CSD, were identified. All patients provided written informed consent, and the institutional review board approved the conduct of this study.

All patients underwent comprehensive evaluations according to an interdisciplinary protocol that guided them through neu-

TABLE 3. Diagnostic criteria for chronic subjective dizziness (4,32)

These symptoms may be described as:

- A. Rocking, swaying, or wobbling that is usually not apparent to others.
- B. A feeling that the floor is moving or wavy.
- C. Lightheaded, foggy or cloudy in the head.
- D. Heavy headed or full in the head.
- E. Spinning "inside the head" without a perception of movement of the visual surround.
- F. A feeling of dissociation from the environment.
- Hypersensitivity to motion—chronic (≥3 mo) hypersensitivity
 to one's own motion, which is not direction specific, and to the
 movement of objects in the environment.
- 3. Visual dizziness (a.k.a. visual vertigo)—exacerbation of symptoms in settings with complex visual stimuli, such as displays in grocery stores or shopping malls, or when performing precision visual tasks (e.g., reading or working on a computer).

rotologic, neurologic, behavioral medicine, and physical therapy evaluations, and audiometric, vestibular laboratory, and radiographic testing as indicated. All patients did not necessarily undergo all examinations or tests, but individuals with symptoms suggesting MD, VM, or MDVM underwent neurotologic/ neurologic consultations, audiometric and vestibular testing, and neuroimaging at a minimum. A predetermined set of variables was abstracted from medical records and entered into a research database, including demographics, clinical history, examination findings, and results of testing. Clinical variables included descriptions of dizziness, sensitivity to self-motion, difficulty with visual complexity, hearing loss and other otologic symptoms (e.g., tinnitus), headache or migraine features, and personal and family neurotologic histories. Examinations included otologic, neurologic, and psychiatric examinations, oculomotor and vestibular ocular reflex examinations with and without fixation, dynamic visual acuity, head impulse testing and positional testing, and observations for nystagmus induced by horizontal and vertical headshake without fixation, Valsalva, or mastoid vibration. Laboratory data included audiometric assessment of pure tone average (PTA) per the AAO-HNS standards for MD studies (11). Tympanograms, acoustic reflexes, and word discrimination scores were measured. Patients were assigned to AAO-HNS hearing class per previously published guidelines (34). Vestibular assessments included oculomotor testing, infrared videonystagmography (VNG) recordings during positional, positioning, hyperventilation, caloric, and rotary chair testing, cervical vestibular evoked myogenic potentials, and platform posturography (Sensory Organization Test), or the Clinical Test of Sensory Integration and Balance. The Dizziness Handicap Inventory (35) and the Hospital Anxiety and Depression Scale (HADS) (36) were used for patient self-reporting of dizziness related handicap, anxiety and depression, respectively.

A consensus conference of dizziness sub-specialists reviewed database entries and rendered final study diagnoses based on the AAO-HNS definition of MD (11), second edition of International Classification of Headache Disorders (ICHD-II, IHS) (37) criteria for migraine with and without aura, Neuhauser criteria for definite and probable VM (19), and peer-reviewed CSD criteria (31). These diagnoses were not mutually exclusive, except that definite VM could not be diagnosed in the absence of ICHD-II migraine. Patients were given diagnoses of MD and VM (i.e., MDVM) when they met diagnostic criteria for both illnesses. Phonophobia during vertigo attacks was not regarded as a migraine symptom, because it was difficult to distinguish this from hyperacusis seen with MD. Patients were excluded from the study if they had a history of severe congenital hearing loss, autoimmune hearing loss, otosyphilis, vertebrobasilar insufficiency or stroke, retrocochlear neoplasm, or basilar migraine.

Statistical Analysis

Statistical analysis proceeded in 3 steps. First, subjects were divided into mutually exclusive MD, MDVM, and VM groups. The presence or absence of CSD was not considered in making group assignments. Bivariate group differences in independent variables were examined by pair-wise and 3-way comparisons using the Kruskal-Wallis one-way analysis of variance (non-parametric method) and the chi-square test. Next, for each independent variable that was significantly different (p < 0.05) between groups on either pair-wise or 3-way comparisons, its sensitivity, specificity, and sensitivity index (d') for separating one diagnostic group from the others were calculated. Finally, independent variables with the highest d' were entered into multivariate logistic regression analyses to identify the model with the greatest ability to predict disease category (VM, MDVM,

^{1.} Subjective unsteadiness or dizziness—persistent (≥3 mo) sensations of unsteadiness or nonvertiginous dizziness that are present on most days

or MD) as measured by areas under the receiver operating characteristic (ROC) curves for each diagnosis. This model was compared against diagnostic criteria for MD and VM. All analyses were performed with SAS v9.1 and JMP v9.0 software (SAS Institute, Cary, NC, USA).

RESULTS

Fifty-five patients were diagnosed with definite or probable MD alone and 71 patients were diagnosed with definite or probable VM alone. Twenty-one patients met criteria for both MD and VM and were placed in the MDVM category. Diagnostic characteristics of patients in the 3 groups are given in Table 4. Six patients (8%) in the VM group had class B or C hearing with diminished PTA, word discrimination or both. Two had conductive hearing loss, and thus, did not meet MD audiometric criteria. The other 4 had bilateral, gradual onset, symmetric, high frequency SNHL that predated their vestibular symptoms by many years and they had very little hearing loss progression after the onset of vertigo or dizziness. This was much more consistent with presbycusis than MD; hence, these patients were placed in the VM group. Seven patients in the MD group reported potentially migrainous events such as severe HA with nausea and vomiting, or photophobia, but did not meet full criteria for migraine (37) or probable VM (19), in part, because of difficulty with retrospective recall of past vestibular and headache events, or vertigo and migrainous symptoms that did not coincide. Ten MD patients had first degree relatives diagnosed with migraine or VM and seven others had strong histories of motion sickness. Taken together, 24/55 (44%) patients in the MD group had one or more migraine indicators though they did not meet VM criteria. When evaluating all 76 patients in our combined group with Ménière's disease (MD+MDVM), 59% (45/76) had vestibular migraine, migraine symptoms, or migraine risk factors along with their MD.

Several significant differences were found among VM, MDVM, and MD groups on bivariate analyses (Tables 5-7). Older age at illness onset and male sex favored MD, whereas younger age at illness onset and female sex favored VM which matches some MD and migraine demographic studies (30). The vast majority of patients with MD reported vertigo attacks lasting several hours. Just over one-third of patients with VM had vertigo attacks lasting several hours, but the vertigo duration could range from seconds to days; consequently, there was a statistically significant association of hourslong attacks with MD. Otologic symptoms (e.g., fluctuating hearing loss, tinnitus, aural fullness), diminished performance on audiometric measurements (e.g., PTA, discrimination), and evidence of peripheral vestibular deficits on physical exam or laboratory testing (e.g., headshake induced nystagmus, caloric asymmetry) were significantly associated with a diagnosis of MD, but did not distinguish between the MD and MDVM groups. Conversely, a history of recurrent moderate to severe headaches and other common symptoms of migraine (e.g. photophobia) during vestibular symptom episodes were significantly associated with a VM diagnosis, but did not distinguish between the VM and MDVM groups. Overall, MDVM appeared to be a hybrid of MD and VM. The only unique features of MDVM were a higher prevalence of a family history of vertigo or dizziness and a greater rate of perceived bilateral hearing loss than either MD or VM alone (Tables 4–5).

The results of multivariate logistic regression analyses are shown in Table 8. The first model tested the discriminative ability of the AAO-HNS criteria for Ménière's disease (11). In pair-wise comparisons, objectively measured hearing loss identified Ménière's disease (MD or MDVM), excluding VM alone. Tinnitus significantly

TABLE 4. Characteristics of patients in the 3 diagnostic groups

		MD (n = 55)		MD	OVM (n = 21)	VN	M (n = 71)	
Episodes of simultaneous vestibular and aural symptoms	Yes	28 (51)	Bilateral 10 (18) Unilateral 18 (33)	9 (43%)	Bilateral 6 (29) Unilateral 3 (14)	27 (38%)	Bilateral 17 (24) Unilateral 10 (14)	
	No	21 (38)	` ′	10 (48)	` ′	40 (56)	` ′	
	Unknown	7 (12)		2 (9)		4 (6)		
Strictly unilateral ear symptoms (anytime)		, í	31 (56)		7 (33)	` `	23 (32)	
Bilateral ear symptoms (anytime)			19 (35)		$13 (62)^a$		29 (41)	
Bilateral MD diagnosis			5 (9)		3 (14)		NA	
MD category	Definite		48 (80) ears		18 (75) ears		NA	
	Probable		12 (20) ears		6 (25) ears			
MD stage	Stage 1		1 (2) ear 0 (0)		0 (0) ears	NA		
	Stage 2		5 (10) ears		1 (6) ear			
	Stage 3		33 (69) ears		15 (83) ears			
	Stage 4		9 (19) ears		2 (11) ears			
Migraine type ^b	Without aura		NA		18 (86) ^a		$42 (59)^a$	
	With aura				$3(14)^a$		$(41)^a$	
VM category	Definite		NA		8 (38)		36 (51)	
	Probable				13 (62)		35 (49)	

Values in parentheses are in percentages.

MD indicates Ménière's disease; MDVM, Ménière's disease with concomitant vestibular migraine; NA, not applicable; VM, vestibular migraine.

^aStatistically significant (p < 0.05).

^bHeadache meets 2004 ICHD-II criteria for migraine.

 TABLE 5.
 Demographics, audiovestibular symptoms, family history, and self-ratings by diagnostic group

		Disease			p value		Sensi	Sensitivity and specificity	ificity	Sens	Sensitivity index (d')	(d')
Variable	VM = 71	MDVM (n = 21)	MD (n = 55)	VM versus MD	VM versus MDVM	MDVM versus MD	VM	MDVM	MD	VM	MDVM	MD
Demographic data	1			1	1		;	į			;	
Race (Caucasian)	62 (87%)	19 (90%)	49 (89%)	0.76	0.7	6.0	NA	NA	NA	NA	ΥN	NA
Sex (female)	59 (83%)	12 (57%)	19 (35%)	< 0.0001	0.013	0.07	83%/29%	57%/38%	35%/23%	1.182	-0.129	-1.124
Age onset (yr)	41	42	51	0.0007	0.71	0.07	ΝΑ	NA	NA	NA	ΝΑ	NA
Illness duration	6 months	1 year	1 year	< 0.0001	0.007	0.338	ΝΑ	NA	NA	NA	ΝΑ	NA
Vestibular symptoms		•	•									
Vertigo duration (h)	19 (38%)	14 (70%)	47 (90%)	< 0.0001	0.04	60.0	38%/15%	70%/36%	90%/23%	-1.342	0.166	1.357
Unsteadiness	49 (92%)	16 (100%)	44 (86%)	0.31	0.26	0.11	92%/10%	100%/11%	%9/%98	0.124	1.1	-0.474
Dizziness (nonvertiginous)	38 (78%)	5 (50%)	25 (50%)	0.0044	0.07	_	78%/50%	50%/36%	50%/27%	0.772	-0.358	-0.613
Auditory symptoms												
Fluctuating HL	9 (14%)	13 (62%)	43 (78%)	<0.0001	< 0.0001	0.14	14%/26%	62%/57%	78%/75%	-1.724	0.482	1.447
Progressive HL	14 (22%)	18 (86%)	51 (93%)	< 0.0001	< 0.0001	0.34	22%/9%	86%/46%	93%/63%	-2.113	0.98	1.808
Tinnitus	37 (55%)	18 (86%)	53 (96%)	<0.0001	0.014	60.0	55%/7%	86%/26%	%88/%96	-1.35	0.437	1.445
Aural fullness	33 (51%)	14 (67%)	43 (78%)	0.0026	0.227	0.3	51%/25%	67%/37%	78%/45%	-0.649	0.108	0.647
Otalgia	17 (27%)	4 (24%)	9 (17%)	0.09	0.75	0.4	27%/82%	24%/78%	17%/73%	0.303	0.066	-0.341
Hearing loss related to vertigo	8 (44%)	4 (22%)	21 (43%)	0.91	0.16	0.12	44%/63%	22%/55%	43%/67%	0.181	-0.647	0.264
Tinnitus related to vertigo	13 (50%)	7 (39%)	27 (59%)	0.47	0.47	0.15	50%/47%	39%/44%	29%/55%	-0.075	-0.43	0.353
Aural fullness related to vertigo	16 (70%)	7 (50%)	24 (65%)	0.71	0.23	0.33	70%/39%	50%/33%	65%/47%	0.245	-0.44	0.31
Family history												
Family history of vertigo/dizziness	16 (30%)	10 (56%)	7 (17%)	0.16	0.04	0.002	30%/72%	%9L/%95	17%/63%	0.058	0.857	-0.622
Family history of hearing loss	11 (25%)	8 (44%)	13 (33%)	0.74	0.19	0.35	25%/64%	44%/73%	33%/69%	-0.316	0.462	0.056
Other												
Mean DHI score	51	40	41	0.02	0.03	0.76	NA	NA	NA	NA	ΝΑ	NA
HADS (abnormal)	32 (48%)	6 (32%)	22 (45%)	0.58	0.11	0.26	48%/59%	32%/53%	45%/56%	0.177	-0.392	0.025
Comorbid CSD	29 (41%)	1 (5%)	2 (4%)	<0.0001	0.002	0.82	41%/96%	2%/75%	4%/76%	1.52	-0.97	-1.044

Gray shaded boxes mark variables with statistical significance (p < 0.05) in the 3-way multivariate logistical regression analysis; bold p values are significant in bivariate analysis. CSD indicates chronic subjective dizziness; DHI, Dizziness Handicap Index; HADS, Hospital anxiety and depression scale.

 IABLE 6.
 Headache-related variables by diagnostic group

		Disease			p value		Sensit	Sensitivity and specificity	ificity	Sen	Sensitivity index (d')	x (d')
Headache variable	VM	MDVM = 21	MD = 55	VM Sussey	VM Wersus MDVM	MDVM versus MD	MA	MADVM	LW.	MA	MADAM	Ę
Treatment variable	(1/ 11)	(17 11)	(CC II)	ALISES INTO	Versus IVID VIVI	TAI SHE IA	TATA	IVID V IVI	OIM.	TATA	IND V INI	divi.
History motion sickness	23 (51%)	6 (32%)	8 (20%)	0.0023	0.15	0.3	51%/77%	32%/64%	20%/55%	0.764	-0.109	-0.716
Migrainous sensory symptoms	37 (95%)	15 (94%)	12 (29%)	<0.0001	0.87	<0.0001	95%/23%	94%/39%	29%/5%	1.72	1.275	-2.198
occurring with vestibular symptoms												
HA	(%66) 02	20 (95%)	38 (81%)	0.0026	0.46	0.14	99%/15%	%8/%56	81%/2%	1.29	0.24	-1.176
HA age of onset (years)	28	34	23	0.44	0.91	0.5	ΝΑ	NA	NA	NA	NA	NA
HA frequency (daily or weekly)	42 (67%)	9 (47%)	6 (19%)	<0.0001	0.31	0.008	%0L/%L9	47%/49%	19%/38%	0.964	-0.1	-1.183
HA Duration (days)	24 (43%)	3 (21%)	2 (8%)	0.0012	0.23	0.4	43%/87%	21%/68%	8%/61%	0.95	-0.339	-1.126
HA severity (mod/severe)	42 (96%)	(%69) 6	5 (26%)	<0.0001	0.02	0.04	%95/%96	69%/25%	26%/10%	1.902	-0.179	-1.925
Photophobia w/ HA	57 (86%)	18 (90%)	14 (40%)	<0.0001	0.67	0.0003	86%/42%	%08/%06	40%/12%	0.878	0.757	-1.428
Phonophobia w/HA	42 (82%)	1 (50%)	10 (63%)	0.1	0.25	0.7	82%/39%	50%/22%	63%/28%	0.636	-0.772	-0.251
Nausea/vomit w/ HA	42 (72%)	14 (82%)	7 (20%)	<0.0001	0.41	<0.0001	72%/60%	82%/47%	20%/25%	0.836	0.84	-1.516
Triggers for HA	29 (69%)	4 (31%)	3 (11%)	<0.0001	0.01	0.11	%83%69	31%/54%	11%/40%	1.45	-0.395	-1.48
Balance symptoms with HA	47 (81%)	14 (82%)	9 (31%)	0.07	0.42	0.03	81%/50%	82%/36%	31%/19%	0.878	0.557	-1.374
Frequency of balance symptoms with HA (most/some of time)	45 (80%)	14 (82%)	8 (29%)	<0.0001	0.59	0.002	80%/49%	82%/37%	29%/19%	0.817	0.586	-1.431
Aura	23 (62%)	4 (25%)	7 (22%)	0.0003	0.007	8.0	62%/77%	25%/57%	22%/49%	1.044	-0.498	-0.797
Family history of migraine	36 (61%)	12 (60%)	11 (26%)	0.0017	96.0	0.016	61%/63%	60%/54%	26%/39%	0.611	0.354	-0.923

Gray shaded boxes mark variables with statistical significance (p < 0.05) in the 3-way multivariate logistical regression analysis; bold p values are significant in bivariate analysis

differed between MD alone and VM alone. The presence of vertigo attacks or aural fullness did not discriminate among any groups. In the 3-way analysis, the AAO-HNS MD criteria excluded VM, almost solely based on the absence of hearing loss. These criteria did not have sufficient sensitivity or specificity to separate MD from MDVM. The second model tested the discriminative ability of the revised Neuhauser vestibular migraine criteria (19). A personal history of migraine and the presence of migrainous features (e.g. photophobia) during episodic vestibular symptoms identified vestibular migraine (VM or MDVM), excluding MD alone. As in the AAO-HNS Ménière's disease criteria model, the presence of vertigo attacks had little discriminative value. Migraine triggers proved not to be a useful distinguishing feature. The most discriminative logistic model, as measured by the largest areas under the ROCs for each diagnosis, confirmed that documented SNHL and a history of recurrent moderate to severe headaches were the most distinguishing features of MD and VM, respectively. Two laboratory tests separated MD from MDVM on this study cohort. Caloric directional preponderance favored MDVM over MD, whereas an abnormal summary classification of the rotary chair test favored MD over MDVM, resulting in a model quite capable of making a 3-way discrimination among the diagnostic groups. The small numbers of subjects in each group with abnormal test results suggest that this particular finding be viewed with caution until re-examined in a larger investigation.

Thirty-two patients were diagnosed with CSD. Nearly all of them (29/32, 91%) were in the VM group. Two (4%) patients with MD and one (5%) patient with MDVM also had CSD. This differential association was significant in bivariate analyses, but did not contribute to the best multivariate discriminative model.

DISCUSSION

In this study of consecutive patients evaluated in a tertiary dizziness clinic, 28% of patients diagnosed with MD also had VM and 23% of patients with VM also had MD. An additional 31% of MD patients had migrainous features in their clinical histories, but did not fulfill all diagnostic criteria for VM. An additional 8% of VM patients had hearing loss that required some effort to recognize as inconsistent with MD. How these patients are categorized might explain some of the variation in the concurrence of MD and VM as reported in the medical literature (12,30,38). From a clinical standpoint, the results of this study suggest that MDVM is not a rare occurrence and must be considered when planning treatment interventions, particularly for patients with atypical or seemingly treatment resistant cases of recurrent vertigo. The rates of comorbidity in primary care settings are not known. The finding that MD and VM are highly coincident is not a new concept. The lifetime prevalence of migraine in MD patients is 56%. Not all of these individuals would have VM, but the rate of migraine was significantly greater than

 TABLE 7. Physical examination and laboratory test results by diagnostic group

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		Disease			p value		Sensiti	Sensitivity and specificity	cificity	Sensiti	Sensitivity index (d')	(q,)
X V = -15 - 15 - 15 - 15 - 15 - 15 - 15 - 1	MV	MDVM	MD	VM	WW	MDVM	377.4	N. S. C. S.	9	7774	70301	9
уапаріе	(n = 7.1)	(n = 21)	(cc = u)	versus IMD	versus MID v M	versus MD	VIM	MDVM	MD	V IM	MDVM	MID
Physical examination												
Headshake nystagmus (abnormal)	9 (15%)	14 (70%)	28 (62%)	< 0.0001	<0.0001	0.55	15%/35%	70%/65%	62%/71%	-1.42	0.91	98.0
Head thrust (abnormal)	2 (3%)	(%62) 9	16 (37%)	< 0.0001	0.0017	0.3	3%/99%	29%/83%	37%/89%	-1.47	0.40	06.0
Nystagmus with mastoid vibration (abnormal)	7 (12%)	7 (35%)	25 (60%)	<0.0001	0.03	0.17	12%/48%	35%/68%	60%/82%	-1.23	80.0	1.17
Smooth pursuit (abnormal)	5 (8%)	3 (14%)	2 (5%)	0.09	0.43	0.18	8%/92%	14%/93%	%06/%5	0	0.40	-0.36
Saccades (abnormal)	(%0) 0	1 (5%)	2 (5%)	0.46	60.0	0.98	%56/%0	%86/%5	%66/%5	-0.68	0.41	0.68
Vestibular testing												
Mean caloric asymmetry (%)	13%	30%	33%	< 0.0001	0.02	0.75	NA	NA	NA	NA	NA	NA
Caloric asymmetry (abnormal)	12 (17%)	12 (63%)	37 (69%)	< 0.0001	0.0001	0.67	17%/33%	%09/%89	69%/73%	-1.39	0.59	1.11
Mean directional prep. (%)	13%	21%	19%	0.09	0.11	0.58	NA	NA	NA	NA	NA	NA
Directional prep. (abnormal)	5 (15%)	(46%)	13 (29%)	0.15	0.03	0.24	15%/67%	46%/77%	29%/76%	-0.60	0.64	0.15
Rotary chair phase (abnormal)	5 (18%)	8 (47%)	34 (68%)	<0.0001	0.04	0.12	18%/37%	47%/50%	68%/71%	-1.25	-0.08	1.02
Rotary chair gain (0.01 Hz)	0.36	0.28	0.25	< 0.0001	0.03	0.48	NA	NA	NA	NA	NA	NA
Rotary chair symmetry (abnormal)	8 (29%)	2 (12%)	18 (35%)	0.02	0.91	0.07	29%/71%	12%/67%	35%/78%	0	-0.74	0.39
Rotary chair summary (abnormal)	8 (29%)	8 (47%)	41 (82%)	< 0.0001	0.21	0.005	29%/27%	47%/37%	82%/64%	-1.17	-0.41	1.27
Posturography (SOT composite)	16 (27%)	5 (33%)	21 (42%)	0.1	0.1	69.0	27%/60%	33%/66%	42%/72%	-0.36	-0.03	0.38
VEMP (abnormal)	9 (16%)	8 (57%)	14 (45%)	0.0068	0.03	0.46	16%/51%	57%/74%	45%/76%	-0.97	0.82	0.58
Audiometry												
$PTA \ge 25 \text{ dB initial}$	10 (7%)	19 (83%)	50 (83%)	0.0011	0.0001	0.3	7%/17%	%69/%88	83%/82%	-2.43	1.45	1.87
$PTA \ge 25 \text{ dB worst}$	12 (9%)	24 (100%)	(100%)	< 0.0001	<0.0001	0.79	%0/%6	100%/63%	100%/78%	-3.67	5.66	3.10
Discrimination ≤85% initial	3 (2%)	14 (61%)	37 (63%)	<0.0001	0.015	0.21	2%/38%	61%/79%	63%/89%	-2.36	-0.80	1.56
Discrimination $\leq 85\%$ worst	3 (2%)	19 (86%)	51 (86%)	< 0.0001	<0.0001	0.52	2%/14%	86%/72%	%98/%98	-3.13	1.66	2.16
Change in discrimination	0.02 ± 0.14	-0.48 ± 3.7	0.6 ± 2.0	0.0002	0.31	0.88	NA	NA	NA	NA	NA	NA
(%/month—mean ± standard												
deviation)												
Hearing class (initial class B–D)	6 (5%)	20 (83%)	42 (71%)	<0.0001	<0.0001 0.0001	0.57	5%/25%	83%/74%	71%/83%	-2.32	1.60	1.51
Hearing loss pattern (low tone)	(%0) 0	23 (90%) 10 (42%)	24 (40%)	<0.001	<0.0001	0.32	%09/%0	42%/82%	40%/71%	3.20 -2.84	0.71	0.3
(J J 6	(6.12)	(2.1.)	(6 (5 .) .]) 				

Gray shaded boxes mark variables with statistical significance (p < 0.05) in the 3-way multivariate logistical regression analysis; bold ρ values are significant in bivariate analysis. Disc. indicates word discrimination score; NA, not applicable; PTA, pure tone average (500, 1,000, 2,000, and 3,000 Hz); SOT, sensory organization test; VEMP, vestibular evoked myogenic potential.

TABLE 8.	Multivariate	logistic	analysis:	pairwise	and 3-way	comparisons	by diagno	ostic group
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Criteria	Variables	VM	versus MD	VM ve	ersus MDVM	MDVN	M versus MD	3-way	comparison
Criteria	variables	p	ROC (AUC)	p	ROC (AUC)	p	ROC (AUC)	p	ROC (AUC)
Ménière's	Vertigo	NS	0.957	NS	0.948	NS	0.675	0.028	VM 0.947
disease criteria	Hearing loss (objective)	0.0001		0.0001		NS		0.0001	MD 0.847 MDVM
	Aural fullness Tinnitus	0.0041 NS		NS NS		NS NS		NS NS	0.755
Vestibular migraine criteria	Episodic vertigo	0.050	0.981	NS	a	NS	0.973	NS	VM 0.992 MD 0.986
	Migraine diagnosis	0.0001		_		0.0001		0.047	MDVM
	Migraine characteristics during vestibular symptoms	0.0005		NS		0.0045		NS	0.878
	Migraine triggers	NS		NS		NS		0.013	
Best model	Headache (moderate/severe)							0.0005	VM 1.00 MD 0.997
	Caloric (directional preponderance)							0.0019	MDVM 0.996
	Rotary chair (abnormal summary)							0.015	
	Audiometry (initial PTA)							0.0001	

Values equal to or greater than 0.9 are marked in bold italics. These occur when sensitivities and specificities both exceed 0.80.

NS indicates not significant; ROC (AUC), receiver operating characteristic area under the curve.

in matched controls and far more than the population prevalence (12).

No single clinical feature or vestibular test finding was able to adequately separate MD, VM, and MDVM. A history of progressive hearing loss and documented poor PTA were the most sensitive and specific for MD, but did not distinguish between MD and MDVM. Other audiologic data such as poor word discrimination and hearing loss patterns also separated VM from MD and MDVM which is due to the hearing loss criteria in the MD definition. However, neither word discrimination or hearing loss pattern (low-tone, high-tone, flat) were significantly different between MD and MDVM. A history of recurrent moderate to severe headaches was the most sensitive and specific for VM, but did not distinguish between VM and MDVM. The full diagnostic criteria for MD and VM were less sensitive and specific than these core diagnostic features. Furthermore, some diagnostic criteria were not helpful at all. The most common duration of vertigo episodes for all groups was several hours, though VM was associated with vertigo episodes lasting for seconds to days, a finding previously reported (2,22). A history of fluctuating hearing loss and progressive hearing loss was reported by 14% and 22% of VM patients, respectively, even though audiograms failed to show hearing loss that met MD criteria. If we consider all patients with VM including those with MDVM, then the rate of subjective fluctuating hearing loss and progressive hearing loss increases to 24% (22/92) and 35% (32/92), respectively. Rates of bilateral perceived hearing loss were not statistically different between VM (17%) and MD (28%). Tinnitus and aural fullness were present in many of the patients in all 3 diagnostic groups. Although the rate of bilateral tinnitus was not different between VM and MD, the incidence of bilateral aural pressure was greater in VM than MD (33% vs. 19%). Migrainous triggers were more common in VM and MDVM than in MD, but did not add diagnostic clarity in the regression model of VM criteria (Table 8). Interestingly, the temporal relationship between aural and vestibular symptoms was not helpful at all in distinguishing between any of the 3 diagnostic groups. These results suggest that future studies are needed to validate and clarify the definitions of MD and VM with particular attention to diagnostic criteria that may be ambiguous in cases of comorbidity. Additionally, perhaps greater awareness of the unique and ambiguous features of MD and VM may improve subject selection criteria for the next generation of clinical and mechanistic investigations of these disorders.

Vestibular testing was not as useful for separating the 3 diagnostic groups. Evidence of a peripheral vestibular deficit favored MD, but did not separate MD from MDVM. The inclusion of caloric directional preponderance and rotary chair summary classification in the best logistic regression model (Table 8) may be an artifact of this study cohort as there is no a priori reason that these 2 parameters should be able to distinguish MD from MD co-existing with VM. Twelve (17%) VM patients in this study had caloric asymmetries exceeding 25% (maximum 63%). None had otologic histories to explain these findings such as vestibular neuritis symptoms. Other abnormal vestibular test results among VM patients included 8 (11%) with rotary chair abnormalities and 12 (17%) with elevated or absent VEMP responses, 5 (7%) of which were bilateral. Previous studies have identified reduced vestibular response and abnormal directional preponderance on caloric testing in

^aUnreliable calculation because of fewer than 5 cases in at least 1 category.

migraine patients without vestibular symptoms (39,40) and in 10%–25% of patients with VM tested during interictal periods (29,41,42). Published guidelines have stated that reduced vestibular response should not exceed 50% in VM alone (43). This was true for most subjects in the VM group, although 2 had caloric asymmetries >60% without any evidence of MD. Platform posturography was not helpful as a distinguishing tool. Perhaps emerging diagnostic modalities such as the ocular VEMP, cervical vestibular evoked myogenic potentials tuning curves, and intratympanic gadolinium enhanced MRI scans will be better for VM, MDVM, and MD categorization. Electrocochleography may be another measure to consider, but its low sensitivity and specificity for MD alone limits its potential (44).

Two findings were more prevalent in the MDVM group than in MD or VM alone: complaints of bilateral hearing loss and a family history of dizziness. It is possible that patients with MDVM reported hearing changes in both ears because migraine is more likely than MD to cause bilateral or alternating hearing symptoms or that both conditions contributed to the total burden of aural symptoms. This study did not include in-depth familial genetic evaluations, but a previous report identified familial migraine, episodic vertigo, and MD (25). In the MDVM group, the development of migraine headache preceded the diagnosis of MD in 75% of patients by an average of 16 years. This study identified 5 patients with MDVM and had documented progression from VM alone to MDVM. They initially had VM with class A hearing, but subsequent audiograms showed significant declines in hearing consistent with MD development. The majority of VM patients with follow-up audiograms did not have deterioration of their PTA to meet MD criteria (11) or discrimination score to less than 80% (89-month mean audiogram follow-up) and, thus, did not move to the MDVM category. This sequence is consistent with a 9-year prospective study of definite and probable VM patients (45). Those authors observed the onset of progressive hearing loss leading to the additional diagnosis of MD in 8 (11%) of their subjects, raising the possibility that VM could be a risk factor for later MD development or that the 2 conditions share predisposing risk factors but manifest at different ages. In the present study, the clinical manifestations of MDVM seemed to be a hybrid of MD and VM features, not a unique clinical entity. Thus, MD and VM were treated as distinct causes of episodic vertigo, but their phenotypes partially overlapped. It remains to be seen if MDVM simply reflects the partially ambiguous overlap of current definitions of MD and VM or MDVM represents a shared pathophysiologic process.

CSD was identified almost exclusively in patients with VM alone. Of the 2 patients with CSD and MD, both had migrainelike symptoms that did not meet diagnostic criteria for migraine (37) or VM (19). This was somewhat surprising because a prospective study of patients with MD treated with intratympanic gentamicin found that 16% developed a CSD-like picture during 1-year follow-up, despite achieving excellent vertigo control (46). Alter-

natively, a prospective observation of medical-psychiatric comorbidity in patients with other vestibular disorders found a CSD presentation to be significantly more likely to develop in patients with VM than MD (47). Pending future investigations of CSD comorbidity in VM and MD, it is worth noting that CSD has been mistaken clinically for ongoing peripheral vestibular disease in patients with MD and vestibular neuritis leading to vestibular ablative procedures that may be unnecessary and potentially aggravate patients' symptoms. The high rate of comorbidity between VM and CSD raises questions about the sensitivity and specificity of current definitions and the potential for shared pathophysiologic mechanisms that parallel the situation with MD and VM.

CONCLUSION

Large overlaps exist in audiovestibular symptoms, neurotologic examinations, and laboratory testing in patients with MD, VM, and MDVM. This complicates clinical diagnosis and treatment. The presence of PTA deterioration favors a diagnosis of MD, whereas a history of recurrent moderate-to-severe headaches favors VM. Neither of these eliminates the situation of coexisting MD and VM, so vigilance is warranted to identify MDVM. CSD was identified much more frequently with VM than MD or MDVM but can confound the assessment of persistent vestibular symptoms in patients with any of these conditions. Reevaluations of current diagnostic criteria for MD, VM, and CSD are needed to reduce ambiguity and account for comorbidity. These conditions may share common pathophysiologic processes, but future studies will have to address this hypothesis.

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