Differences in characteristics between definite vestibular migraines, migraines with vestibular symptoms that do not meet vestibular migraine criteria, and migraines without vestibular symptoms: A cross-sectional study through the lens of central sensitization

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Research Article

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Abstract

**Background:** The demographic and clinical characteristics of vestibular migraine (VM) based on the International Classification of Headache Disorders (ICHD)-III beta are not well documented, and the underlying pathophysiology remains largely unknown. Based on evidence that central sensitization is involved in VM pathogenesis, we hypothesized that cutaneous allodynia (CA), which is a clinical manifestation of central sensitization, and interictal widespread pressure hyperalgesia (IWPH), which may be an accelerator for central sensitization, are more frequently associated with VM patients compared with non-VM patients. The aim of this study was as follows: 1) to assess differences in demographic and clinical characteristics among VM patients, patients with migraine with vestibular symptoms not meeting VM criteria (MwVS), and patients with migraine without vestibular symptoms (MwoVS); and 2) to evaluate whether VM patients were more frequently associated with CA/IWPH compared with the other two groups.

**Methods:** This cross-sectional study enrolled consecutive migraine patients, aged 18–65. The comprehensive interview form included diagnostic questions of migraine and VM, demographic characteristics, migraine-specific variables, migraine-associated symptoms, and CA. IWPH occurrence was investigated using a manual tender point survey and clinical parameters were compared.

**Results:** A total of 245 episodic migraineurs (mean age = 39.5 ± 11.3 years, 81.2% women) were enrolled. Based on ICHD-III beta criteria, 65 (26.5%), 74 (30.2%), and 106 (43.3%) patients were assigned to the VM group, MwVS group, or MwoVS group, respectively. Pairwise comparisons demonstrated no significant differences between the VM and MwVS groups, except for higher occurrence of headache disability in the VM group. Compared with the MwoVS group, the VM group was significantly associated with aura, severe disability, depression, tinnitus, sleep disorders, multimodal CA, and IWPH.

**Conclusions:** There were no significant differences in clinical features between VM and MwVS groups, except for disability, which was possibly caused by criteria selection bias. VM and MwVS may be on the same disease process spectrum. Widespread multimodal CA, including clinical manifestations of thalamic sensitization, was significantly associated with VM patients compared with MwoVS patients, which indicates that thalamic sensitization may play a key role VM pathogenesis. Furthermore, IWPH may enhance susceptibility to thalamic sensitization.

**Background**

Vestibular migraine (VM) is the common cause of episodic vertigo/dizziness [1–3]. However, research on VM is limited, because this subtype is defined using relatively new diagnostic criteria, which was proposed by the Barany Society and the International Headache Society in 2012 [4]. Therefore, the demographic and clinical characteristics as well as pathophysiology remain largely unknown [5, 6].

Migraineurs commonly complain of multisensorial hypersensitivity, including photophobia phonophobia, osmophobia, allodynia, and hyperalgesia. The migraine brain seems to be “hyperresponsive” to sensory
stimuli [7]. In addition, patients with VM develop hypersensitivity to vestibular and visual stimuli, which are characterized by heightened self-motion sensitivity and visually induced dizziness [8]. Central and peripheral sensory systems are sensitized in migraine disease [9–11], yet there is evidence that central sensitization plays a stronger role in VM pathophysiology [12–14]. We hypothesized that VM patients are more centrally sensitized, as evidenced by more frequently occurrences of cutaneous allodynia (CA), which is a clinical manifestation of central sensitization [15], compared with non-VM patients. Previous studies have suggested that dysfunction of the brainstem descending pain modulatory center induces central sensitization during migraine attacks [16] and leads to interictal widespread thermal [17] and pressure [18] hyperalgesia. Interictal widespread pressure hyperalgesia (IWPH) is marked by a strong pain induced interictally by potentially noxious pressure throughout the body due to a reduced pressure pain threshold [18]. Comparing the prevalence of CA and IWPH between the VM non-VM migraine patients may provide pathophysiological insights into the development of VM.

The purpose of this study was as follows: 1) to assess the differences in demographic and clinical characteristics among VM, migraine with vestibular symptoms not meeting VM criteria (MwVS), and migraine without vestibular symptoms (MwoVS); and 2) to evaluate whether VM is more strongly associated with CA/IWPH compared with the other two groups. To the best of our knowledge, this is the first report that investigated the difference in CA frequency, including allodynia subtypes, and IWPH between VM and non-VM migraine patients.

Methods

Study design and setting

Migraineurs were recruited for the cross-sectional survey from January 2018 to December 2019 at Toriyama Clinic. All subjects participated in a standardized interview, and careful clinical examinations were conducted by the first author to assess the patients based on the inclusion and exclusion criteria. This study was approved by the institutional review board of Shinshu University School of Medicine (approval number 3552-1).

All patients provided informed consent prior to enrolment in the study.

Participants

Consecutive patients with a chief complaint of headache were considered eligible for inclusion in this study based on the following inclusion criteria: migraine as defined by the International Classification of Headache Disorders (ICHD)-III beta criteria [4], aged 18–65 years, and migraine illness for ≥ 6 months. Key exclusion criteria were as follows: comorbid diagnosis of headaches due to underlying pathology or trauma, use of drugs that could confound interpretation of the study results, headache induced by medication overuse, and migraine with major depressive disorder. All patients were permitted to take abortive migraine drugs.

Clinical evaluation
The comprehensive interview form included diagnostic questions based on the ICHD-III beta criteria for the diagnosis of migraine and VM, demographic characteristics, migraine-specific variables, and migraine-associated symptoms. Diagnosis of vestibular symptoms, vertigo, and/or dizziness, was performed according to the International Classification of Vestibular Disorders of the Barany Society [19]. Migraine-specific variables included the migraine subtype, age at onset, duration of migraine illness, duration of migraine attacks, migraine attack frequency, headache intensity, headache disability, and family history of migraines. Migraine-associated symptoms included nausea and/or vomiting, photophobia, phonophobia, osmophobia, depression, tinnitus, sleep disorders, acute CA, and IWPH. Medication usage was assessed based on clinical history. No information about the menstrual cycle was obtained for female patients in this study. Based on the diagnostic criteria, patients were assigned to three migraine subtypes: 1) VM group, 2) MwVS group, or 3) MwoVS group. All diagnostics and procedures were conducted by the first author.

**Headache intensity**

The headache intensity was assessed using a numerical rating scale [20], with 0 representing “no pain” and 10 representing “the worst imaginable pain.”

**Headache disability**

Headache Impact Test-6 (HIT-6) [21] was used to measure headache-related disability.

**Depression**

Depressive symptoms were evaluated by the self-rating depression scale [22]. Patients with a self-rating depression scale score ≥ 48 were diagnosed with depression their [23].

**Tinnitus and sleep disorder**

Tinnitus and sleep disorders were evaluated using the following Yes/No questions.

1. During a headache, do you perceive tinnitus that you did not notice between headaches?
2. Do you have trouble falling asleep and/or staying asleep?

**Cutaneous allodynia**

The comprehensive migraine questionnaire, which was proposed Ashkenazi et al. [24], included 16 questions regarding allodynia symptoms. The questionnaire was as follows:

Do you experience pain or unpleasant sensations on your skin during a migraine attack when you engage in any of the following activities? (Answer “Yes,” “No,” or “Not Applicable.”): (1) Combing your hair; (2) Pulling your hair back (example: ponytail); (3) Shaving your face; (4) Wearing eyeglasses; (5) Wearing contact lenses; (6) Wearing earrings; (7) Wearing necklaces; (8) Wearing anything tight on your head or neck (hat, scarf); (9) Wearing anything on your arm or wrist (bracelet, watch); (10) Wearing a finger ring; (11) Wearing tight clothes; (12) Being covered by a heavy blanket; (13) Taking a shower (when shower water hits your face); (14) Resting on a pillow with your face using the side of your head with the
headache; (15) Being exposed to heat (examples: cooking, placing heating pads on your face); (16) Being exposed to cold (examples: breathing through your nose on a cold day, placing ice packs on your face).

To assess extracephalic CA, three additional questionnaire items, which were proposed by Guy et al. [25], were conducted as follows:

Do you experience pain or unpleasant sensations during a migraine attack when you engage in any of the following activities: (17) Taking a shower (when shower water hits your skin on areas other than the face); (18) Being exposed to heat on areas other than the face; and (19) Being exposed to cold on your skin on areas other than the face.

Thus, the allodynia questionnaire consisted of 19 questions. Patients who responded with “Yes” to at least two of these items were defined as allodynic [24].

Cephalic and extracephalic cutaneous allodynia

Cephalic CA was assessed using questions (1), (2), (3), (4), (5), (6), (7), (8), (13), (14), (15), and (16). Patients who responded with “Yes” to at least one of these items were defined as cephalic CA [25]. Extracephalic CA was evaluated using questions (9), (10), (11), (12), (17), (18), and (19). Patients who responded with “Yes” to at least one of these items were defined as extracephalic CA [25].

Mechanical and thermal cutaneous allodynia

Mechanical CA was assessed using questions (1), (2), (4), (5), (6), (7), and (11). Patients representing at least one of these items were defined as mechanical CA [11, 26]. Thermal CA was evaluated using questions (14), (15), (16), (18), and (19). Patients representing at least one of these items were defined as thermal CA [11, 26].

Interictal widespread pressure hyperalgesia

For patients who were consulted interictally (72 or more hours after the last migraine attack), IWPH was assessed using the manual tender point survey, which has also been used in fibromyalgia diagnosis as a practical alternative for quantitative sensory testing [18, 27]. This procedure was performed by the first author before the migraine subtype diagnosis. The sum of the positive tender points was used to identify scores that were above the cutoff thresholds set at \( \geq \) moderate pain, which was defined as the tender point count (TPC). The maximum TPC was 18 (9 designated spots × right/left). A manual tender point survey was performed by the first author systematically over 18 fibromyalgia tender points based on the published guidelines [27]. Patients were defined as migraine with IWPH when they scored \( 7 \geq \) TPC [18].

Statistical analysis

Descriptive data are expressed as means ± standard deviation or percentages. When comparing the three groups for continuous variables with normal distribution, one-way analysis of variance tests were performed. For nonparametric conditions, the median of continuous variables was compared with a Kruskal–Wallis test. Chi-square analysis was performed to determine the difference between the frequencies of categorical variables. Upon reaching a significant result, Bonferroni or Steel-Dwass
multiple comparisons test were used for post-hoc analysis, when appropriate. All \( p \)-values were two-tailed, and \( p < 0.05 \) was statistically significance. No statistical power calculation was conducted prior to this study. The sample size was based on the available data. The odds ratio (OR) and 95% confidence intervals (CI) were determined. The effect size for continuous variables was calculated using Cohen’s \( d \). All statistical analyses were performed with the free software, EZR ver. 1.40 [28].

**Results**

A total of 291 patients were potentially eligible migraineurs during the study period. Forty-six patients were excluded from the study due to comorbidity of tension-type headache (n = 8), occipital neuralgia (n = 3), chronic lumbar pain (n = 1), fibromyalgia (n = 1), sleep apnea (n = 1), use of drugs that could confound the interpretation of study results (valproic acid, pregabalin, and/or duloxetine) (n = 8), headache induced by medication overuse (n = 16), major depressive disorder (n = 4), and patients for whom some variables were missing (n = 4). Once the evaluations were complete, 245 episodic migraineurs (mean age = 39.5 ± 11.3 years, 81.2% women) were enrolled in the study. Of the 245 patients, 65 (26.5%), 74 (30.2%), and 106 (43.3%) patients were assigned to the VM group, MwVS group, or MwoVS group, respectively. Vestibular symptoms were identified in 139 (56.7%) of migraineurs. Patients who were assigned to the MwVS group included two patients with vestibular symptoms with a duration of < 5 minutes, 36 patients with mild vestibular symptoms, and 36 patients not meeting both the duration and disability criteria. Interictal consultations of 102 patients were performed, followed by evaluations for the presence of IWPH.

Table 1 compares the baseline demographic and clinical characteristics among the three groups. Variables with significantly different values among the three groups were as follows: female gender (\( p = 0.027 \)), migraine with any aura (\( p = 0.004 \)), migraine with visual aura (\( p = 0.035 \)), migraine intensity (\( p = 0.032 \)), headache disability (\( p = 0.002 \)), prevalence of depression (\( p < 0.001 \)), migraine with tinnitus (\( p < 0.001 \)), prevalence of sleep disorders (\( p = 0.005 \)), and migraine with CA (\( p = 0.011 \)). Of the patients who experienced migraine with aura, five experienced only sensory aura. Pairwise comparisons showed significantly high values in the VM group compared with the MwoVS group, for the following variables: migraine with aura (\( p = 0.007, \text{OR} = 2.78, 95\% \text{ CI} = 1.41–5.57 \)), migraine with visual aura (\( p = 0.049, \text{OR} = 2.78, 95\% \text{ CI} = 1.15–4.53 \)), HIT-6 (\( p = 0.028, \text{Cohen’s } d = 0.20 \)), prevalence of depression (\( p = 0.001, \text{OR} = 4.38, 95\% \text{ CI} = 1.84–10.96 \)), migraine with tinnitus (\( p < 0.001, \text{OR} = 7.17, 95\% \text{ CI} = 3.03–18.27 \)), prevalence of sleep disorders (\( p = 0.011, \text{OR} = 3.96, 95\% \text{ CI} = 1.48–11.49 \)), and migraine with CA (\( p = 0.025, \text{OR} = 2.64, 95\% \text{ CI} = 1.27–5.72 \)). Post-hoc comparison revealed significantly high values in the MwVS group compared with the MwoVS group for the following variables: migraine with tinnitus (\( p = 0.01, \text{OR} = 3.53, 95\% \text{ CI} = 1.45–9.10 \)) and prevalence of sleep disorders (\( p = 0.036, \text{OR} = 3.36, 95\% \text{ CI} = 1.26–9.65 \)). Comparisons between the VM and MwVS groups showed no significant differences, except for the HIT-6 score (\( p = 0.003, \text{Cohen’s } d = 0.28 \)), which was significantly high in the VM group compared with the MwVS group.
Table 1
Comparison of variables among the VM, MwVS, and MwoVS groups

| Variables                      | VM (n = 65) | MwVS (n = 74) | MwoVS (n = 106) | p value | Pairwise comparisons (p value) |
|--------------------------------|-------------|---------------|-----------------|---------|-------------------------------|
|                                |             |               |                 |         | VM-MwoVS                      |
|                                |             |               |                 |         | MwVS-MwoVS                    |
|                                |             |               |                 |         | VM-MwVS                       |
| General variables              |             |               |                 |         |                               |
| Female                         | 56 (86.2%)  | 65 (87.8%)    | 78 (73.6%)      | 0.027   | 0.242 b                       |
|                                |             |               |                 |         | 0.097 b                        |
|                                |             |               |                 |         | 1.000 b                        |
| Age, years                     | 39.1 ± 11.1 | 40.0 ± 11.0   | 39.5 ± 11.7     | 0.895   | NA                            |
|                                |             |               |                 |         | NA                            |
|                                |             |               |                 |         | NA                            |
| Migraine-specific variables    |             |               |                 |         |                               |
| Migraine with aura             | 37 (56.9%)  | 27 (36.5%)    | 34 (32.1%)      | 0.004   | 0.007 b                       |
|                                |             |               |                 |         | 1.000 b                        |
|                                |             |               |                 |         | 0.075 b                        |
| Migraine with visual aura      | 33 (50.8%)  | 27 (36.5%)    | 33 (31.1%)      | 0.035   | 0.049 b                       |
|                                |             |               |                 |         | 1.000 b                        |
|                                |             |               |                 |         | 0.382 b                        |
| Age at migraine onset, years   | 19.7 ± 8.3  | 20.4 ± 9.6    | 20.8 ± 9.1      | 0.726   | NA                            |
|                                |             |               |                 |         | NA                            |
|                                |             |               |                 |         | NA                            |
| Migraine duration, years       | 19.4 ± 11.5 | 19.6 ± 11.0   | 18.7 ± 10.8     | 0.867   | NA                            |
|                                |             |               |                 |         | NA                            |
|                                |             |               |                 |         | NA                            |
| Duration of headache attack, hours | 24.4 ± 29.8 | 31.1 ± 53.0  | 20.4 ± 24.6    | 0.932   | NA                            |
|                                |             |               |                 |         | NA                            |
|                                |             |               |                 |         | NA                            |
| Frequency of headache, attacks/month | 3.39 ± 3.62 | 3.37 ± 4.32  | 3.08 ± 3.75    | 0.935   | NA                            |
|                                |             |               |                 |         | NA                            |
|                                |             |               |                 |         | NA                            |
| Headache intensity (NRS)       | 7.95 ± 1.58 | 7.28 ± 1.57  | 7.41 ± 1.43     | 0.032   | 0.081 e                       |
|                                |             |               |                 |         | 1.000 e                        |
|                                |             |               |                 |         | 0.052 e                        |
| Headache disability (HIT-6)    | 63.2 ± 6.50 | 59.7 ± 6.83  | 60.4 ± 6.92     | 0.002   | 0.028 e                       |
|                                |             |               |                 |         | 0.669 e                        |
|                                |             |               |                 |         | 0.003 e                        |
| First-degree relative FH       | 36 (55.4%)  | 49 (66.2%)    | 63 (59.4%)      | 0.412   | NA                            |
|                                |             |               |                 |         | NA                            |
|                                |             |               |                 |         | NA                            |
| Migraine-associated symptoms   |             |               |                 |         |                               |
| Nausea/vomiting                | 65 (100%)   | 71 (95.9%)    | 102 (96.2%)     | 0.329   | NA                            |
|                                |             |               |                 |         | NA                            |
|                                |             |               |                 |         | NA                            |
| Variables                          | VM (n = 65) | MwVS (n = 74) | MwoVS (n = 106) | p value | Pairwise comparisons (p value) |
|-----------------------------------|-------------|---------------|----------------|---------|------------------------------|
|                                   |             |               |                |         | VM-MwoVS                    |
|                                   |             |               |                |         | MwVS-MwoVS                  |
|                                   |             |               |                |         | VM-MwVS                     |
| Photophobia                       | 60 (92.3%)  | 61 (82.4%)    | 87 (82.1%)     | 0.114 f | NA                           |
|                                   |             |               |                |         | NA                           |
|                                   |             |               |                |         | NA                           |
| Phonophobia                       | 54 (83.1%)  | 55 (74.3%)    | 78 (73.6%)     | 0.145 a | NA                           |
|                                   |             |               |                |         | NA                           |
|                                   |             |               |                |         | NA                           |
| Osmophobia                        | 43 (66.2%)  | 42 (56.8%)    | 54 (50.9%)     | 0.326 a | NA                           |
|                                   |             |               |                |         | NA                           |
|                                   |             |               |                |         | NA                           |
| Depression (SDS ≥ 48)             | 22 (33.8%)  | 13 (17.6%)    | 11 (10.4%)     | < 0.001 a | 0.001 b                  |
|                                   |             |               |                |         | 0.722 b                |
|                                   |             |               |                |         | 0.133 b                |
| Tinnitus                          | 28 (43.1%)  | 20 (27%)      | 10 (9.4%)      | < 0.001 a | < 0.001 b            |
|                                   |             |               |                |         | 0.011 b                |
|                                   |             |               |                |         | 0.212 b                |
| Sleep disorders                   | 16 (24.6%)  | 16 (21.6%)    | 8 (7.5%)       | 0.005 a | 0.011 b                |
|                                   |             |               |                |         | 0.036 b                |
|                                   |             |               |                |         | 1.000 b                |
| Acute cutaneous allodynia         | 50 (76.9%)  | 52 (70.3%)    | 59 (55.7%)     | 0.011 a | 0.025 b                |
|                                   |             |               |                |         | 0.203 b                |
|                                   |             |               |                |         | 1.000 b                |
| Medication                        |             |               |                |         |                             |
| Use of acute medication           | 43 (66.2%)  | 41 (55.4%)    | 69 (65.1%)     | 0.323 a | NA                       |
|                                   |             |               |                |         | NA                       |
|                                   |             |               |                |         | NA                       |
| Use of triptan                    | 32 (49.2%)  | 48 (64.9%)    | 51 (48.1%)     | 0.062 a | NA                       |
|                                   |             |               |                |         | NA                       |
|                                   |             |               |                |         | NA                       |
| No medication                     | 1 (1.5%)    | 3 (4.1%)      | 4 (3.8%)       | 0.733 f | NA                       |
|                                   |             |               |                |         | NA                       |
|                                   |             |               |                |         | NA                       |

Values represent absolute numbers with corresponding percentages or means ± SD.

Bold italics indicate significant p-values (p < 0.05).

FH, family history; HIT-6, headache impact test; MwoVS, migraine without vestibular symptoms; MwVS, migraine with vestibular symptoms but not meeting vestibular migraine criteria; NA, not applicable; NRS, numeric rating scale; SDS, self-rating depression scale; VM, vestibular migraine

a $\chi^2$-test

b Bonferroni test

c One-way analysis of variance
Table 2 compares each CA subtype among the three groups. There was a significant difference in the association rate of each CA subtype: cephalic CA ($p = 0.007$), extracephalic CA ($p = 0.003$), mechanical CA ($p = 0.013$), and thermal CA ($p = 0.005$). The VM group had a significantly high rate of association compared with the MwoVS group for all CA subtypes: cephalic CA ($p = 0.019$, OR = 3.34, 95% CI = 1.38–9.03), extracephalic CA ($p = 0.004$, OR = 3.02, 95% CI = 1.50–3.23), mechanical CA ($p = 0.027$, OR = 2.71, 95% CI = 1.27–6.11), and thermal CA ($p = 0.034$, OR = 2.35, 95% CI = 1.20–4.67). (Table 2). Compared with the MwoVS group, the MwVS group was significantly associated with thermal CA ($p = 0.026$, OR = 2.34, 95% CI = 1.22–4.51). Comparisons between the VM and MwVS groups showed no significant differences for any of the CA subtypes ($p > 0.05$).
Table 2
Comparison of the frequency of CA subtypes among the VM, MwVS, and MwoVS groups

| Alodynia subtypes | VM (n = 65) | MwVS (n = 74) | MwoVS (n = 106) | p value | Pairwise comparisons (p value) |
|-------------------|-----------|-------------|----------------|--------|-------------------------------|
|                   |           |             |                |        | VM-MwoVS | MwVS-MwoVS | VM-MwVS |
| Cephalic CA       | 57 (87.7%)| 60 (81.1%)  | 72 (67.9%)     | 0.007  | 0.019 b | 0.219 b | 1.000 b |
| Extracephalic CA  | 46 (70.8%)| 43 (58.1%)  | 47 (44.3%)     | 0.003  | 0.004 b | 0.287 b | 0.508 b |
| Mechanical CA     | 52 (80.0%)| 54 (73.0%)  | 63 (59.4%)     | 0.013  | 0.027 b | 0.259 b | 1.000 b |
| Thermal CA        | 37 (56.9%)| 42 (56.8%)  | 38 (35.8%)     | 0.005  | 0.034 b | 0.026 b | 1.000 b |

Values represent absolute numbers with corresponding percentages.

Bold italics indicate significant p-values (p < 0.05).

CA: cutaneous allodynia; MwoVS, migraine without vestibular symptoms; MwVS, migraine with vestibular symptoms but not meeting vestibular migraine criteria; VM, vestibular migraine

a χ²-test

b Bonferroni test

Table 3 shows demographic data and a positive rate of IWPH for the 102 patients who underwent the manual tender point survey. Among the three groups, there were no significant differences in the rate of patients who underwent the manual tender point survey, nor for gender or age, whereas a significant difference in the positive rate of IWPH (p = 0.019) was detected. The post-hoc test showed that the VM group was significantly associated with IWPH compared with the MwoVS group (p = 0.044, OR = 4.56, 95% CI = 1.40–16.86).
Table 3
Comparison of the frequency of IWPH among the VM, MwVS, and MwoVS groups

| Variables                        | VM (n = 24/65) | MwVS (n = 34/74) | MwoVS (n = 44/106) | p value | Pairwise comparisons (p value) |
|----------------------------------|---------------|-----------------|-------------------|---------|-----------------------------|
|                                  |               |                 |                   |         | VM-MwoVS | MwVS-MwoVS | VM-MwVS |
| Patients who underwent MTPS, n (%)| 24 (36.9%)    | 34 (45.9%)      | 44 (41.5%)        | 0.581 a | NA         | NA         | NA      |
| Female, n (%)                    | 20 (83.3%)    | 31 (91.2%)      | 32 (72.7%)        | 0.113 a | NA         | NA         | NA      |
| Age (years), mean ± SD           | 42.2 ± 11.6   | 43.0 ± 11.0     | 40.4 ± 11.9       | 0.601 b | NA         | NA         | NA      |
| IWPH, yes (%)                    | 18 (75%)      | 15 (44.1%)      | 18 (40.9%)        | 0.019 a | 0.044 c    | 1.000 c    | 0.115 c |

Bold italics indicate significant p-values (p < 0.05).

IWPH, interictal widespread pressure hyperalgesia; MTPS, manual tender point survey; MwoVS, migraine without vestibular symptoms; MwVS, migraine with vestibular symptoms but not meeting vestibular migraine criteria; NA, not applicable; VM, vestibular migraine

a $\chi^2$-test

b One-way analysis of variance

c Bonferroni test

Discussion

The main findings of this cross-sectional study, which was conducted in a secondary headache clinic, can be summarized as follows: 1) Of the 245 patients, 65 (26.5%), 74 (30.2%), and 106 (43.3%) patients were assigned to the VM group, MwVS group, or MwoVS group, respectively. 2) Variables with significantly different values among the three groups were female gender, migraine with aura, migraine with visual aura, migraine intensity, HIT-6 score, prevalence of depression, migraine with tinnitus, prevalence of sleep disorders, migraine with CA, and migraine with IWPH. 3) Post-hoc pairwise comparison revealed that the VM group was significantly associated with aura, visual aura, headache disability, depression, tinnitus, sleep disorders, CA, and IWPH compared with the MwoVS group. The comparison between the VM and MwVS groups showed no significant differences in variables, except for the HIT-6 score. 4) The frequency of all CA subtypes showed significant differences among the three groups. The VM group was significantly more strongly associated with all CA subtypes compared with the MwoVS group. The MwVS group was significantly more strongly associated with thermal CA...
compared with the MwoVS group. Between the VM and MwVS groups, there was no significant difference in the frequency of CA and IWPH.

**Vestibular migraine prevalence**

Vestibular symptoms were identified in 56.7% of the migraine patients who participated in this study, which was consistent with the proportion observed in previous studies, while dizziness was observed in 51.7–61% of migraine patients [29–31]. VM was observed in 26.5% of the migraine patients in this study, which is more than twice as high as the 9–12% rate reported before the new criteria were developed [2, 29] and the 10.3% reported after the new criteria were established [32]. Calhoun et al. reported that there was a strong correlation between migraines and subjective complaints of vertigo, and that nearly half of the subjects suffered from vertigo or dizziness when the headache intensity was 7 or higher [33]. Based on this result, the high prevalence of VM in this study may be due to selection bias according to the study population used and clinical context at a secondary headache clinic.

**Differences between the VM and MwVS groups**

There were no significant differences in migraine-related variables between the VM and MwVS groups except for the HIT-6 score. It is reasonable that the VM group, which consists of patients with moderate to severe vertigo, showed high disability (i.e., high HIT-6 score) compared with the MwVS group, which consists of patients with mild vertigo, as HIT-6 is a measure of headache disability. Abouzari et al. compared the clinical features of migraine patients with vestibular symptoms between the following two cohorts: the VM cohort corresponding to the VM group in this study and the migraine headache cohort equivalent to the MwVS group in this study [34]. They concluded that the differences between cohorts represent selection bias rather than meaningful features that are unique to the cohorts [34]. Our study supported their conclusion that VM and MwVS may be on a spectrum of the same disease processes. Therefore, to elucidate the VM pathophysiology, it may be appropriate to compare the group that combines the VM group and the MwVS group with the MwoVS group.

**Female gender and vestibular migraine**

Our results showed that the VM group had a female preponderance, which was consistent with a recent report [6]. Moreover, a female preponderance was observed in both the MwVS and MwoVS groups. Female gender was significantly different among the three groups in this study; however, multiple comparisons did not reveal a significant difference. This result could have been caused by an overall female ratio of 81.2%, which is a highly biased variable. Increasing the number of cases is expected to make a significant difference. Studies on experimentally induced pain have reported that women exhibited greater pain sensitivity, enhanced pain facilitation, and reduced pain inhibition compared with men [35]. The female gender has been reported to be associated with CA [10, 26, 36, 37]. A higher susceptibility of CA may be influenced by the relationship between female gender and VM.

**Aura and vestibular migraine**

In previous studies, migraine with aura was reported in 13–36% of VM [2, 38]. In this study, the rate of migraine with aura (56.9%) was considerably high. However, this difference was considered to be due to
selection bias caused by our clinic providing neurosurgery, thus attracting a higher number of patients with this migraine with aura. In Japan, many migraine patients with aura tend to undergo neurosurgery, since visual aura is considered a stroke warning.

The correlation between vertigo and migraine with or without aura is epidemiologically controversial. Previous studies found an association between migraine with aura and vertigo [31, 39], whereas other studies have reported that patients with migraine without aura have vertigo more frequently [3, 38, 40–42]. A prospective, cross-sectional study documented a significantly high prevalence of vertigo/dizziness (24.5% vs. 12.1%) in migraine with aura compared with migraine without aura ($p < 0.01$) [33]. Consistent with this view, we found a strong association between migraine with aura and the VM group. In the present study, post-hoc pairwise comparisons revealed that aura was significantly associated with the VM group compared with the MwoVS group ($p = 0.007$). In addition, visual aura was significantly associated with the VM group compared with the MwoVS group ($p = 0.049$). Meanwhile, there was no significant difference in migraine with aura ($p = 1.000$) and visual aura ($p = 1.000$) between the MwVS and MwoVS groups. These results provide a reasonable basis for assuming that aura plays an important role throughout the VM stage. Vestibular symptoms in VM patients can be explained by cortical spreading depression (CSD) [43]. Demarquay et al. suggested that the vestibular aura (vertigo/dizziness) be classified as a typical migraine aura, which is the clinical consequence of the CSD-induced transient dysfunction of the parieto-insular vestibular cortex [44]. The significant association between the VM group and visual aura suggests that vestibular aura might develop when CSD from the occipital lobe propagates to the adjacent vestibular cortex, or by the opposite propagation. Interestingly, aura but not photophobia was significantly associated with the VM group, can be explained by the involvement of the cuneus and lingual gyrus in photophobia [45] and the possible origin of a typical visual aura in V3A [46]. In addition, aura is reportedly associated with CA [11, 36, 37]. Our results show that acute CA was significantly associated with the VM group compared with the MwoVS group. Therefore, aura may play an important role in VM.

**Headache intensity and vestibular migraine**

There have been few studies on the association between VM and headache intensity. Kutay et al. reported no significant difference in headache between a VM group and a migraine without vertigo group [47]. Conversely, Calhoun et al. reported a strong correlation between migraine pain and the subjective complaint of vertigo, and headache intensity of 7 or greater was concomitant with vertigo or dizziness in almost half of the subjects [36]. Furthermore, headache intensity was found to be associated with CA [11, 37]. In this study, headache intensity was highest in the VM group and was significantly different among the three groups. However, no significant difference was found between each pair in the multiple comparison, which may be due to an insufficient number of cases showing statistical significance. Vestibular nuclei receive a projection from the trigeminal nucleus [48], and trigeminal nerve stimulation causes nystagmus in patients with migraine, which indicates increased vestibular severity excitability compared with the healthy controls [49]. Recently, Zhang et al. demonstrated the sensitization of vestibular nucleus neurons for impairing vestibular function in an induced chronic migraine rat model [50]. Stronger trigeminal nerve inputs may have contributed to stronger sensitization of vestibular nuclei.
Therefore, the significant difference in headache intensity among the three groups in this study as well as the highest intensity being observed in the VM group were reasonable. The pathophysiology of VM vestibular symptoms may involve a modulation of vestibular signals through vestibular pathways, including vestibular nuclei, which are sensitized by severer headaches.

Headache disability and vestibular migraine

The HIT-6 score is a reliable and validated tool for assessing headache-related disability. In this study, a post-hoc comparison revealed that the HIT-6 score was significantly high in the VM group compared with the MwVS group and MwoVS group. Intuitively, the HIT-6 score may be not a variable that is related to VM pathophysiology, but it may have been enhanced by the impact of vertigo-associated migraine. The ICHD-III beta criteria for VM with moderate to severe vestibular symptoms lasting between 5 minutes and 72 hours will identify patients who have a more debilitating type of migraine. In addition, headache disability has been reported to be associated with CA [10, 11, 37].

Depression and vestibular migraine

The prevalence of depression was significantly different among the three groups. A post-hoc comparison revealed that the prevalence of depression was significantly higher in the VM group than in the MwoVS group. Migraine, vestibular disorder, and psychological disorders such as anxiety and depression are all closely related [47, 51, 52]. Furman et al. conceptualized this overlap of migraine, anxiety, and balance disorder as migraine-anxiety related dizziness (MARD). The pathophysiology of MARD probably relates primarily to monoaminergic pathways, which are important for migraine, anxiety, the central vestibular system, and their interconnections [53]. VM may be a subtype of MARD in which vestibular disorders predominate the three components. Depression has also been correlated with CA in migraine disease [11, 18, 36, 54].

Tinnitus and vestibular migraine

Recent studies have reported tinnitus in 35.3–52.6% of VM patients [55–57]. In this study, tinnitus was found in 43.1% of VM patients, which did not conflict with previous reports. Tinnitus was significantly associated with VM and MwVS groups compared with the MwoVS group. There was no significant difference in the frequency of tinnitus between the VM and MwVS groups. Tinnitus is related to aberrant neural activity at certain levels of the auditory system [58], which makes it difficult to identify the sites that are responsible for tinnitus. Several potential mechanisms, including the cortical pathway, subcortical pathway, and peripheral pathway, have been proposed for the pathophysiological interaction between tinnitus and migraine.

Possible cortical pathway responsible for tinnitus

Phonophobia may be associated with cortical hypersensitivity in the auditory cortex, which is involved in the processing of sound [59]. Our results show that there was no significant difference in the frequency of phonophobia between the VM and MwoVS groups. Therefore, it seems unlikely that tinnitus is due to hypersensitivity originating from the auditory cortex. In patients with VM, tinnitus may occur when CSD extends secondarily to the auditory cortex.
**Possible subcortical pathway responsible for tinnitus**

The medial geniculate body, which is a potential target for tinnitus treatment [60], may be associated with tinnitus in VM patients. Despite having a primary role in auditory signaling from the cochlear nucleus, the medial division of the medial geniculate body receives projections from the spinal cord [61] and vestibular nuclei [62, 63]. Therefore, in VM patients, the medial geniculate body may receive spinal cord input of amplified somatic pain represented by CA and/or IWPH. Moreover, the medial geniculate body may receive input from vestibular nuclei sensitized by headache input from the trigeminal nerve [48]. When the auditory cortex receives modified auditory inputs via the medial geniculate body sensitized by somatic pain and vestibular inputs, VM patients may be aware of tinnitus. Previous studies have suggested that in approximately 6–12% of normal-hearing persons with tinnitus and spontaneous otoacoustic emissions (SOAEs), the SOAEs are partly responsible for tinnitus [64]. In VM patients, SOAEs that are modulated through the sensitized subcortical auditory pathway, including the medial geniculate body, may be involved in tinnitus.

**Possible peripheral pathway responsible for tinnitus**

The trigeminovascular system innervates the inner ear [65]. Trigeminal terminals on the cochlear artery may release the calcitonin gene-related peptide [66] and substance P [67] in a manner that is similar to what occurs in the dural artery during a migraine [68]. This process promotes vasodilation and plasma extravasation via inflammatory mediators [69] and may be related to endolymphatic hydrops in the inner ear, thus resulting in vertigo, and tinnitus. These pathways may play a role in the vertigo, hypoacusis, and tinnitus experienced by some migraineurs during their migraine attacks, and which can mimic Meniere's disease [70]. Since ~ 50% of patients with Meniere's disease also meet the criteria for migraine [71, 72], tinnitus could be related to a specific subtype of Meniere's disease [73]. Volcy et al. found a temporal association between the onset and improvement of CA and tinnitus, which suggests that both tinnitus and CA may share a similar pathophysiological mechanism. They assumed that abnormal auditory cortex functioning due to central and/or peripheral sensitization may contribute to the development of tinnitus in patients with migraine, and that tinnitus may be another allodynic symptom in some patients [74]. According to this sensitization hypothesis, tinnitus may be a migraine symptom.

**Sleep disorders and vestibular migraine**

Consistent with previous studies [75, 76], sleep disorders were significantly high in the VM group compared with the MwoVS group. Sleep disorders can trigger VM headaches, as well as migraine headaches [2, 77]. Allodynia is strongly related to sleep quality, in a bi-directional way; sleep disturbances may favor central sensitization, and, in turn, allodynia may impair sleep [78].

**Allodynia and vestibular migraine**

Our results revealed that CA was significantly associated with the VM group. To date, studies on the association between VM and allodynia have been sparse. Based on the ICHD-II criteria, Akdal et al. revealed that allodynia occurred significantly more frequently in migraine patients with vestibular symptoms (n = 663) than in migraine patients without vestibular symptoms (n = 208) (p = 0.001) [31].
Abouzari et al. documented no significant differences in allodynia frequency between definite VM (n = 104) diagnosed by the ICHD-III beta criteria and non-VM migraine (n = 100) patients ($p = 0.350$) [34]. To the best of our knowledge, this is the first report that is based on the ICHD-III beta criteria to reveal that all CA subtypes (cephalic, extracephalic, thermal, and mechanical CA) were significantly more strongly associated with VM patients compared with MwoVS patients. In brief, VM was strongly associated with “widespread multimodal allodynia.” The development of cephalic CA indicates sensitization of the second-order spinal trigeminal nucleus, whereas extracephalic CA may reflect sensitization of third-order trigeminovascular neurons in the posterior thalamus [7]. Using functional magnetic resonance imaging assessment of blood oxygenation level-dependent signals, Burstein et al. revealed that the spread of multimodal allodynia beyond the locus of the headache is mediated by sensitized thalamic neurons that process nociceptive information from the cranial meninges together with sensory information from the head and whole body [79]. Radiological investigations in humans have demonstrated multiple projections from vestibular nuclei to the thalamus. [63]. We assume that, in VM, vestibular inputs modulated through the thalamus, which are sensitized by repeated headaches that form the vestibulo-thalamo-cortical pathway, are conducted through the cortex and cause vestibular symptoms.

Determining the presence or absence of widespread multimodal allodynia may be supportive of VM diagnosis. The emphasized relationship between CA and VM can be interpreted in different ways. Central sensitization induced by a recurrent headache can simultaneously induce a distortion of cutaneous sensitivity (CA) and spatial perception (vertigo). Alternatively, recurrent stimuli of vertigo in subjects with hypersensitivity to vestibular symptoms may, in cooperation with repetitive headaches, induce central sensitization. Previous studies reported that the average time between the onset of headache and the onset of vestibular symptoms is 8 to 19 years [39, 80]. Given that migraines begin earlier than migrainous vertigo in most patients [2, 42], it is reasonable to assume that thalamic sensitization due to headaches is part of the pathophysiology underlying vestibular symptoms of migraine. In a similar speculation as that of Volcy et al., who assumed that tinnitus would be an allodynic symptom [74], we assume that abnormal vestibular cortex functioning due to thalamic sensitization may contribute to the vertigo development in patients with migraine and that vertigo may be another allodynic symptom in some patients.

**IWPH and vestibular migraine**

To date, this is the first report revealing a significantly stronger association between VM patients and IWPH compared with MwoVS patients. The pathophysiology of interictal widespread thermal and pressure hyperalgesia may involve the brainstem descending pain modulatory system [18, 81]. Dysregulation of the descending pain modulatory system, which may underlie the pathophysiology of IWPH [18], might play an important role in amplifying headache input to the thalamus, thus accelerating thalamic sensitization. Sensitized thalamus may develop into a widespread multimodal CA. IWPH with acute CA, which are clinical manifestations of central sensitization, as evidenced by increases in frequency that were correlated with each other [18].

**Candidate brain region of vertigo in migraine**
Based on the above discussion, we hypothesized that vertigo in VM consists of three distinct origins: 1) vertigo originating cortically, which may be a possible focal symptom due to CSD; 2) vertigo originating subcortically, which may be related to the modulation of vestibular input by the sensitized thalamus; 3) vertigo originating peripherally, which may be related to Meniere's disease-like inner ear disorders. Among them, clinical manifestation of thalamic sensitization, which is a widespread multimodal CA, was specifically associated with VM, which indicates that thalamic sensitization may play a key role in VM pathogenesis. The presence of IWPH may be involved in susceptibility to thalamic sensitization, as it may indicate a brain state that facilitates noxious trigeminal input (headache) to reach the thalamus.

**Strengths and limitations**

The strengths of this study include a large cohort size, well-defined migraine status, detailed information on migraine-associated symptoms, and detailed descriptions about allodynia. An objective finding that was associated with the impaired descending pain modulatory system, IWPH, was investigated in a practical and reproducible manner using a manual tender point survey without quantitative sensory testing. However, this study had limitations. First, patients were recruited from a secondary headache clinic seeking further medical therapies for headache rather than vertigo. Thus, refractory patients who visited a tertiary headache center or patients with mild headaches that improved with conventional therapies were likely excluded from the cohort. In addition, migraine patients who visited an otolaryngology department with a chief complaint of moderate to severe vertigo may have been excluded from this study. The headache intensity and disability of our cohort may have been biased toward a homogenized moderate or more severe state, while those of vertigo may have been biased toward a homogenized moderate or less severe state, compared to those who were treated in the general population. This biased population may have limited the generalizability of the results and conclusions. Second, because our data were collected through a questionnaire for the headache population, recollection bias regarding the nature and intensity of vestibular symptoms is a potential limitation. Third, only one rater of IWPH was involved, which may have caused the limitation in of a lack of inter-rater reliability. Fourth, due to the cross-sectional design, we can only describe the association of symptoms. Therefore, we cannot draw firm conclusions about the potential causal relationship between migraine-associated symptoms and vestibular symptoms that meet the diagnostic criteria for VM.

**Generalizability**

Although factors associated with VM in this study can be generalized for patients who visited a secondary headache clinic rather than the general population, the demographic and clinical features of migraine, including prevalence of vestibular symptoms, were consistent with those of previous studies that were conducted in several countries. Further studies are needed to corroborate our findings.

**Directions for future research**

Future research should focus on evaluating whether the results could be replicated by other raters in evaluating cohorts consisting of other nationalities and ethnicities. In collaboration with findings in the fields of otolaryngology and neurology, further research should be conducted to elucidate the relationship between detailed allodynia and detailed vestibular symptoms. Findings that can be obtained with clinical
examinations, including widespread multimodal allodynia/hyperalgesia for patients with vertigo, may provide quality clues, and insights into VM pathophysiology through the lens of central sensitization.

Conclusions

This non-blinded cross-sectional study revealed that VM patients diagnosed based on the ICHD-III beta criteria showed distinctive clinical features compared with MwoVS patients. Variables that were significantly associated with the VM group compared with the MwoVS group were as follows: aura, severe disability, depression, tinnitus, sleep disorders, widespread multimodal CA, and IWPH. There were no significant differences in clinical features between the VM and MwVS groups, except for disability, which may have been caused by criteria selection bias. Due to these similarities, VM and MwVS were speculated to be on a spectrum consisting of the same disease processes. The clinical manifestation of thalamic sensitization, which is a prevalent multimodal CA, was strongly associated with variables that are specifically associated with VM patients, which indicates that thalamic sensitization plays a key role in VM pathogenesis. Furthermore, IWPH may be involved in susceptibility to thalamic sensitization. To the best of our knowledge, this is the first report to show that widespread multimodal CA and IWPH were significantly more strongly associated with VM patients than MwoVS patients.

List Of Abbreviations

CA: Cutaneous allodynia; CI: Confidence intervals; CSD: Cortical spreading depression; HIT-6: Headache Impact Test-6; ICHD: International Classification of Headache Disorders; IWPH: Interictal widespread pressure hyperalgesia; MARD: Migraine-anxiety related dizziness; MwoVS: Migraine without vestibular symptoms; MwVS: Migraine with vestibular symptoms not meeting VM criteria; OR: Odds ratio; SOAEs: Spontaneous otoacoustic emissions; TPC: Tender point count; VM: Vestibular migraine

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board at the Shinshu University School of Medicine (approval number 3552-1). All patients provided informed consent prior to enrolment in this study.

Consent for publication

Not applicable.

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article (and Additional file 1).

Competing interests
The authors declare that they have no competing interests.

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**Authors’ contributions**

TT wrote the first draft. YH did major revisions. All authors contributed to the planning of the study. All authors read and approved the final manuscript.

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