Differences in clinical features between vestibular migraine, migraine with vestibular symptoms, and migraine without vestibular symptoms: A cross-sectional study

Toshihide Toriyama (toriyama@avis.ne.jp)
Toriyama Clinic

Yoshiki Hanaoka
Shinshu University School of Medicine

Tetsuyoshi Horiuchi
Shinshu University School of Medicine

Research Article

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Abstract

Background: Vestibular migraine (VM) is associated with a higher central sensitization than migraines without vestibular symptoms. VM and migraines with vestibular symptoms (MwVS) may share a similar disorder spectrum, as no differences in clinical features have been found, apart from disability. Patients with VM experience fluctuating mechanical pain thresholds and vestibular symptoms even without migraine attacks, suggesting persistent central sensitization. We hypothesized that interictal allodynia or hyperalgesia, which are indicative of persistent central sensitization, could be used to differentiate between VM, MwVS, and migraine without vestibular symptoms, that is, migraine only (MO). This study aimed to compare the demographic and clinical characteristics of VM, MwVS, and MO during the interictal phase and to determine whether VM exhibits more interictal allodynia/hyperalgesia than MwVS and MO.

Methods: In this cross-sectional study, we enrolled consecutive migraineurs aged 18–65 years who were assigned into the VM, MwVS, and MO groups and administered a structured questionnaire comprising diagnostic questions for migraine, VM, and associated variables. Clinical variables were compared among the three groups. After confirming data normality, variables were compared using appropriate tests. A multivariate logistic regression identified significant VM-associated variables, applying backward stepwise selection. Results were considered statistically significant when the two-tailed p-values < 0.05. The presence of interictal widespread pressure hyperalgesia (IWPH) was determined using a manual tender point survey as an alternative to the quantitative sensory testing method, which is the gold standard.

Results: Overall, 163 patients, of which 31 (19%), 54 (33.1%), and 78 (47.9%) were assigned to the VM, MwVS, and MO groups, respectively, were included in this study. Post-hoc comparison revealed that aura, tender point count, and IWPH were significantly associated with VM compared to MwVS. Multivariate logistic regression confirmed that aura and IWPH were independent and significant predictors of VM. No significant differences were observed in clinical features between MwVS and MO.

Conclusions: Aura and IWPH are independent predictors of VM, potentially playing pivotal roles in its pathogenesis. We have identified clinical features that differentiate between VM and MwVS, which can enhance our understanding of VM.

Background

Vestibular migraine (VM) is the second most common cause of episodic vertigo and dizziness [1–4]. However, research on VM is limited due to the relatively new diagnostic criteria proposed by the Barany Society and the International Headache Society in 2012, which define this subtype [5]. Consequently, the demographic and clinical characteristics, as well as pathophysiology, of VM remain poorly understood [6, 7]. Migraineurs report multisensory hypersensitivities, including photophobia, phonophobia, osmophobia, allodynia [8], and hyperalgesia [9–16].
According to previous research, migraineurs’ brains may be hyperresponsive to sensory stimuli [17]. VM could be considered a subtype of migraine with hypersensitivity to self-motion [18]. The peripheral and central nervous systems are sensitized during migraines [8, 19, 20], and central sensitization is evident during VM [21, 22]. Therefore, VM may differ from other migraines in terms of heightened sensitivity of the vestibular pathways, leading to episodic vertigo [23].

According to our previous study [24], compared to migraine without vestibular symptoms, i.e., migraine only (MO), VM showed significantly higher associations with all cutaneous allodynia (CA) subtypes; however, the association between vestibular migraine and CA subtypes and the association between migraine with vestibular symptoms (MwVS) and CA subtypes were not significantly different. Pairwise comparison of VM and MwVS showed no significant differences in clinical features, except for disability that might have been potentially influenced by selection bias, as supported by the findings of Abouzari et al. [25]. Therefore, we concluded that thalamic sensitization [26] plays a crucial role in VM pathogenesis, as it is significantly associated with widespread multimodal CA compared to non-vestibular episodic migraine.

A recent study reported that mechanical pain thresholds in both cephalic and extracephalic regions fluctuate during the migraine cycle. Migraineurs with any type of migraine demonstrate greater sensitivity to mechanical stimuli before, during, and after an attack than in the period in-between attacks [27].

Reportedly, patients with VM experience vestibular symptoms without headaches [28], suggesting that MwVS may be due to persistent central sensitization [29].

Burstein et al. [8] reported that migraine patients experience increased pain sensitivity to both innoxious and noxious stimuli on the skin and scalp during an attack, and this condition is known as CA [30–32] and hyperalgesia [9, 10]. CA is a prevalent symptom in migraines, affecting approximately 60% of patients, and is thought to be a clinical manifestation of central sensitization [8, 33].

Previous studies [20, 32] on alldynia were conducted using quantitative sensory testing. In our previous research, we could not distinguish VM from MwVS using acute alldynia prevalence [24]; however, we hypothesized that interictal alldynia or hyperalgesia, which indicates persistent central sensitization, can be used to differentiate between VM, MwVS, and MO.

Comparing interictal CA and hyperalgesia prevalence between patients with VM and patients with non-VM may offer pathophysiological insights into VM. However, quantitative sensory testing (QST), the gold standard for assessing interictal alldynia and hyperalgesia, may not be applicable in daily practice, as it requires time, special equipment, and expertise [32].

Although validated questionnaires exist for assessing migraine alldynia [20, 31] only few questionnaires have been used to assess hyperalgesia in routine practice without the QST [34]. We proposed a tender point count (TPC)-based test using the manual tender point survey (MTPS), which is used for a fibromyalgia diagnosis, as an alternative to QST for bedside testing to identify interictal widespread
pressure hyperalgesia (IWHP) [35]. Patients with IWHP have intense generalized pain caused by potentially noxious pressure during the interictal period due to reduced pressure pain threshold [33]. A dysfunctional descending pain modulatory system in the brainstem may contribute to central sensitization during attacks [36] and widespread interictal thermal [14] and pressure hyperalgesia [35].

To the best of our knowledge, this is the first study to investigate the difference in the prevalence of interictal allodynia and hyperalgesia between VM and non-VM.

**Methods**

**Aim**

This study aimed to compare the demographic and clinical characteristics of VM, MwVS, and MO during the interictal phase; determine if VM is more allodynic and hyperalgesic than MwVS and MO during the interictal phase; explore any associations between VM and MwVS during the interictal phase; and identify VM-related independent and significant risk factors.

**Design and setting of the study**

In this cross-sectional survey conducted between January 2018 and March 2021, migraineurs were enrolled at the Toriyama Clinic, Komoro, Nagano, Japan.

**Participants**

This study included consecutive migraineurs aged 18–65 years who met the International Classification of Headache Disorders (ICHD)-IIIβ criteria [5] with a history of migraine of at least 6 months. To avoid the influence of acute allodynia, the patients were required to be migraine-free for at least 48 h. Patients with other primary or secondary headaches, neck disorder-related headaches, sinusitis, fibromyalgia, local or systemic diseases-related headache, or incomplete data were excluded. Moreover, those who have taken migraine prophylactic or anti-neuropathic pain agents that could interfere with the results were excluded. However, all the patients were permitted to take abortive migraine medications.

**Clinical evaluation**

The interview included comprehensive diagnostic questions based on the ICHD-IIIβ criteria for migraine and VM diagnosis [5], demographic characteristics, and associated symptoms. Vestibular symptoms, vertigo, and dizziness were diagnosed using the International Classification of Vestibular Disorders of the Barany Society [37].

The patients were grouped into the following three categories: those with VM meeting the ICHD criteria [5], those with migraines and vestibular symptoms not meeting the criteria for VM (MwVS), and those with migraines but without vestibular symptoms (MO).
Migraine-specific variables and associated symptoms were recorded, including age at onset, duration of migraine, headache intensity within the last 3 months, migraine disability assessed using headache impact test-6 (HIT-6), family history of migraine, nausea, vomiting, photophobia, phonophobia, osmophobia, tinnitus, sleep disorders, depression, acute and interictal CA, TPC, and IWPH. Patients’ medication history was recorded; however, information on the menstrual cycle was not collected.

**Measurement**

**Acute CA symptoms**

We used a 16-item allodynia symptom questionnaire adapted from the study by Ashkenazi et al. [31]; this questionnaire comprised 12 questionnaire items from the Allodynia Symptom Checklist (ASC-12) [20] and four additional questions. The patients were asked if they experienced pain or discomfort on their skin during a migraine attack while engaging in certain activities, such as wearing tight clothes or jewelry or being covered by a heavy blanket. The patients who answered “yes” for two or more questionnaire items during or in-between migraine attacks were considered to be allodynic. The three questionnaire items proposed by Guy et al. [38] to assess extracephalic CA symptoms regarding the effect of water, heat, and cold during showers on skin areas other than the face were added to the 16 questionnaire items, resulting in a total of 19 items. The 19-item questionnaire was used according to a previous study [24]; the questionnaire has been provided in detail in Additional File 1.

**Interictal CA**

Individuals who answered “yes” to “do you experience abnormal sensitivity or discomfort outside of headache attacks? [39]” were classified as having interictal CA.

**Cephalic CA and extracephalic CA**

Cephalic and extracephalic CA were assessed using questions proposed by Guy et al. [38]. Participants who answered “yes” to at least one of the questionnaire items were considered to have cephalic or extracephalic allodynia.

**Mechanical and thermal allodynia**

Mechanical and thermal allodynia was assessed in all patients using type-specific survey questions. Positive responses to any mechanical or thermal item determined the presence of each condition [24]. Question categorization as thermal or mechanical was based on consistency with previous large surveys [20, 30].

**Widespread multimodal CA**

Patients with thermal, mechanical, cephalic, and extracephalic CA were classified as having widespread multimodal CA [26].

**IWPH**
MTPS, previously used for fibromyalgia diagnosis [40], was used to assess IWPH. TPC is the sum of positive tender points (TPs) with moderate or greater pain thresholds. Patients with TPC ≥ 7 were classified as migraineurs with IWPH [35]. The first author, T. Toriyama, performed MTPS on 18 TPs before diagnosing VM to avoid potential confirmation bias.

Assessment of headache intensity, disability, depression, tinnitus, and sleep disorders

Headache intensity and headache-related disability were assessed using a numerical rating scale (NRS) [39, 41] and the HIT-6 [40, 42], respectively. Depression symptoms were assessed using a self-rating depression scale (SDS) [43], with an SDS score of ≥ 48 indicating depression [41, 44]. Tinnitus was assessed with a “yes” or “no” response to the question: “during a headache attack, do you perceive tinnitus that you do not notice between headaches?” Sleep disorders were evaluated using a Yes/No questionnaire asking about trouble falling asleep or staying asleep.

Statistical analysis

Data were analyzed using various statistical methods. Continuous variables are presented as means ± standard deviation or percentages, and one-way analysis of variance and Kruskal–Wallis tests were used to compare variables with normal and nonparametric distributions, respectively. The normality of the data was confirmed using the Kolmogorov–Smirnov test. Categorical variables were analyzed using chi-square analysis to compare differences in frequencies. Post-hoc analysis was performed using Bonferroni or Steel–Dwass multiple comparisons tests when necessary. Multivariate logistic regression model was used to identify variables that were independently and significantly associated with VM.

To ensure a comprehensive analysis of important factors in the study, the model included variables with p < 0.2 in the post-hoc comparison, and then, using backward stepwise selection, factors with lower significance (higher P value) were removed until only those with a final P < 0.05 remained in the model. The p-values were two-tailed and p < 0.05 was considered statistically significant. No prior statistical power calculation was performed, as the sample size was based on the available data. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, and Cohen's $r$ was used to determine the effect size for nonparametric analysis. All statistical analyses were performed using the EZR software, version 1.40 [45].

Results

Overall, 205 patients with potential interictal migraine were recruited for the study; however, 42 were excluded owing to comorbidities, missing data, or use of medications that could affect the results. Finally, 163 patients with episodic migraine (mean age, 40.9 ± 11.5 years; women, 78.5%) were enrolled, of which 31 (19%), 54 (33.1%), and 78 (47.9%) were assigned to the VM, MwVS, and MO groups, respectively. Vestibular symptoms were reported by 85 participants. The MwVS group included 23 participants who did not meet the duration criterion and 31 who did not meet both duration and disability criteria. Patients
with vestibular symptom duration of < 5 min reported mild disability that did not last for ≥ 72 h (Fig. 1). Table 1 presents the comparison of demographic and clinical characteristics, while Table 2 presents the comparison of the MTPS results of the three groups. Significant differences were found in aura, osmophobia, tinnitus, acute CA, TPC, and IWPH prevalence. No significant differences were found in sex, age, body mass index, age at migraine onset, duration, attack frequency and duration, headache intensity, family history, nausea/vomiting, photophobia, phonophobia, sleep disorder, depression, and medication use (p > 0.05) between the three groups.
<table>
<thead>
<tr>
<th>Variables</th>
<th>VM (n = 31)</th>
<th>MwVS (n = 54)</th>
<th>MO (n = 78)</th>
<th>p value</th>
<th>Pairwise comparisons (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>VM- MwVS</td>
</tr>
<tr>
<td>General variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>27 (87.1%)</td>
<td>45 (83.3%)</td>
<td>56 (71.8%)</td>
<td>0.123</td>
<td>NA</td>
</tr>
<tr>
<td>Age, years</td>
<td>39.8 ± 12.8</td>
<td>41.5 ± 11.0</td>
<td>40.9 ± 11.5</td>
<td>0.817</td>
<td>NA</td>
</tr>
<tr>
<td>Migraine-specific variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Migraine with aura</td>
<td>22 (71.0%)</td>
<td>22 (40.7%)</td>
<td>30 (38.5%)</td>
<td>0.006</td>
<td>0.042</td>
</tr>
<tr>
<td>Age at migraine onset</td>
<td>21.2 ± 9.3</td>
<td>22.4 ± 10.6</td>
<td>21.2 ± 9.3</td>
<td>0.805</td>
<td>NA</td>
</tr>
<tr>
<td>Migraine duration (years)</td>
<td>19.7 ± 12.1</td>
<td>19.1 ± 11.9</td>
<td>19.7 ± 11.2</td>
<td>0.866</td>
<td>NA</td>
</tr>
<tr>
<td>Duration of headache</td>
<td>15.1 ± 15.3</td>
<td>20.4 ± 19.8</td>
<td>18.8 ± 21.3</td>
<td>0.616</td>
<td>NA</td>
</tr>
<tr>
<td>attack (h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache Frequency</td>
<td>3.9 ± 4.3</td>
<td>2.7 ± 2.6</td>
<td>2.8 ± 2.9</td>
<td>0.607</td>
<td>NA</td>
</tr>
<tr>
<td>(attacks/month)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache intensity (NRS)</td>
<td>7.5 ± 1.6</td>
<td>7.0 ± 1.7</td>
<td>7.3 ± 1.4</td>
<td>0.605</td>
<td>NA</td>
</tr>
<tr>
<td>Headache disability (HIT-6)</td>
<td>62.5 ± 7.4</td>
<td>59.9 ± 7.5</td>
<td>60.1 ± 5.8</td>
<td>0.219</td>
<td>NA</td>
</tr>
<tr>
<td>First-degree relative FH</td>
<td>18 (58.1%)</td>
<td>37 (68.5%)</td>
<td>47 (60.3%)</td>
<td>0.532</td>
<td>NA</td>
</tr>
<tr>
<td>Migraine-associated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>31 (100%)</td>
<td>51 (94.4%)</td>
<td>72 (92.3%)</td>
<td>0.284</td>
<td>NA</td>
</tr>
</tbody>
</table>

Values represent absolute numbers with corresponding percentages or means ± SD. Bold and italicized text indicate significant p-values (p < 0.05). FH, family history; HIT-6, headache impact test; MO, migraine only; MwVS, migraine with vestibular symptoms not meeting vestibular migraine criteria; NA, not applicable; NRS, numeric rating scale; SDS, self-rating depression scale; VM, vestibular migraine. $^a$χ²-test; $^b$ Bonferroni test; $^c$ One-way analysis of variance; $^d$ Kruskal–Wallis test; $^e$ Fisher’s exact test.
<table>
<thead>
<tr>
<th>Variables</th>
<th>VM (n = 31)</th>
<th>MwVS (n = 54)</th>
<th>MO (n = 78)</th>
<th>p value</th>
<th>Pairwise comparisons (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VM- MwVS</td>
</tr>
<tr>
<td>Photophobia</td>
<td>28 (90.3%)</td>
<td>41 (75.9%)</td>
<td>58 (74.4%)</td>
<td>0.178</td>
<td>NA</td>
</tr>
<tr>
<td>Phonophobia</td>
<td>27 (87.1%)</td>
<td>42 (77.8%)</td>
<td>56 (74.4%)</td>
<td>0.254</td>
<td>NA</td>
</tr>
<tr>
<td>Osmophobia</td>
<td>19 (61.3%)</td>
<td>27 (50.0%)</td>
<td>25 (32.1%)</td>
<td>0.011a</td>
<td>1b</td>
</tr>
<tr>
<td>Depression (SDS ≥ 48)</td>
<td>8 (25.8%)</td>
<td>43 (20.4%)</td>
<td>12 (1.4%)</td>
<td>0.436a</td>
<td>NA</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>14 (45.2%)</td>
<td>12 (22.2%)</td>
<td>9 (11.5%)</td>
<td>0.001a</td>
<td>0.148b</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>6 (19.4%)</td>
<td>11 (20.4%)</td>
<td>8 (10.3%)</td>
<td>0.224a</td>
<td>NA</td>
</tr>
<tr>
<td>Acute cutaneous allodynia</td>
<td>25 (80.6%)</td>
<td>33 (61.1%)</td>
<td>41 (52.6%)</td>
<td>0.026a</td>
<td>0.361b</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of acute medication</td>
<td>14 (45.2%)</td>
<td>30 (55.6%)</td>
<td>43 (55.1%)</td>
<td>0.595a</td>
<td>NA</td>
</tr>
<tr>
<td>Use of triptans</td>
<td>19 (61.3%)</td>
<td>33 (61.1%)</td>
<td>46 (48.1%)</td>
<td>0.96a</td>
<td>NA</td>
</tr>
<tr>
<td>No medication</td>
<td>0 (0.0%)</td>
<td>2 (3.7%)</td>
<td>3 (3.8%)</td>
<td>0.545e</td>
<td>NA</td>
</tr>
</tbody>
</table>

Values represent absolute numbers with corresponding percentages or means ± SD. Bold and italicized text indicate significant p-values (p < 0.05). FH, family history; HIT-6, headache impact test; MO, migraine only; MwVS, migraine with vestibular symptoms not meeting vestibular migraine criteria; NA, not applicable; NRS, numeric rating scale; SDS, self-rating depression scale; VM, vestibular migraine. aχ²-test; b Bonferroni test; c One-way analysis of variance; d Kruskal–Wallis test; e Fisher’s exact test
Table 2
Comparison of TPC and IWPH frequency using MTPS between the VM, MwVS, and MO groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>VM (n = 31)</th>
<th>MwVS (n = 54)</th>
<th>MO (n = 78)</th>
<th>p value</th>
<th>Pairwise comparisons (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPC</td>
<td>8.9 ± 3.8</td>
<td>5.4 ± 3.9</td>
<td>4.97 ± 4.2</td>
<td>&lt; 0.001</td>
<td>VM-MwVS &lt; 0.001 &lt; 0.001</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>VM-MO &lt; 0.001 MO-MwVS &lt; 0.001</td>
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<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IWPH, yes (%)</td>
<td>24 (77.4%)</td>
<td>21 (38.9%)</td>
<td>24 (30.8%)</td>
<td>&lt; 0.001</td>
<td>0.002 &lt; 0.001</td>
</tr>
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</tbody>
</table>

Bold and italicized text indicates significant p-values (p < 0.05). IWPH, interictal widespread pressure hyperalgesia; MTPS, manual tender point survey; MO, migraine without vestibular symptoms; MwVS, migraine with vestibular symptoms not meeting the vestibular migraine criteria; NA, not applicable; TPC, tender point count; VM, vestibular migraine. aχ²-test; bKruskal–Wallis test; cBonferroni test; dSteel–Dwass test

The results of post-hoc pairwise comparisons of significant variables between the three groups showed that VM had significantly higher values than MwVS in terms of the frequency of migraine with aura (OR: 3.50, 95% CI: 1.26–10.39), TPC (p < 0.001, Cohen's r = 0.401) and IWPH prevalence (OR: 5.28, 95% CI: 1.80–17.21). Similarly, VM had significantly higher values than MO with respect to the frequency of migraine with aura (OR: 3.78, 95% CI: 1.19–12.85), osmophobia (OR: 5.27, 95% CI: 1.59–19.38), tinnitus (OR: 5.40, 95% CI: 1.39–26.36), acute CA prevalence (OR: 4.33, 95% CI: 1.27–16.7), TPC (OR: not applicable), and IWPH prevalence (OR: 6.94, 95% CI: 2.06–26.26). No significant differences in clinical features were found between MwVS and MO (Tables 1 and 2).

Significant differences were noted in the association of certain CA subtypes among the groups (Table 3). Extracephalic CA (p = 0.008), mechanical CA (p = 0.01), and widespread multimodal CA (p = 0.006) were significantly different between the three groups. Allodynia subtypes did not differ significantly between VM and MwVS or MwVS and MO. In comparison to MO, VM had significantly higher rates of extracephalic CA (p = 0.016, OR: 8.77, 95% CI: 2.03–25.09), mechanical CA (p = 0.021, OR: 8.11, 95% CI: 1.71–149.12), and widespread multimodal CA (p = 0.014, OR: 14.76, 95% CI 2.89–10.39).
Table 3

Comparison of the frequency of CA subtypes between VM, MwVS, and MO groups

<table>
<thead>
<tr>
<th>Allodynia subtypes</th>
<th>VM (n = 31)</th>
<th>MwVS (n = 54)</th>
<th>MO (n = 78)</th>
<th>p value</th>
<th>Pairwise comparisons (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>VM-MwVS</td>
</tr>
<tr>
<td>Cephalic CA</td>
<td>27 (87.1%)</td>
<td>43 (79.6%)</td>
<td>52 (66.7%)</td>
<td>0.052a</td>
<td>NA</td>
</tr>
<tr>
<td>Extracephalic CA</td>
<td>23 (74.2%)</td>
<td>29 (53.7%)</td>
<td>33 (42.3%)</td>
<td>0.008a</td>
<td>0.306b</td>
</tr>
<tr>
<td>Mechanical CA</td>
<td>26 (83.9%)</td>
<td>33 (61.1%)</td>
<td>41 (52.6%)</td>
<td>0.006a</td>
<td>0.152b</td>
</tr>
<tr>
<td>Thermal CA</td>
<td>17 (54.8%)</td>
<td>25 (46.3%)</td>
<td>36 (46.2%)</td>
<td>0.688a</td>
<td>NA</td>
</tr>
<tr>
<td>Widespread multimodal CA</td>
<td>16 (51.6%)</td>
<td>17 (31.5%)</td>
<td>16 (20.5%)</td>
<td>0.006a</td>
<td>0.327b</td>
</tr>
</tbody>
</table>

Values represent absolute numbers with corresponding percentages. Bold and italicized text indicate significant p-values (p < 0.05). CA: cutaneous allodynia; VM, vestibular migraine; MwVS, migraine with vestibular symptoms not meeting the vestibular migraine criteria; MO, migraine only. aχ²-test, b Bonferroni test

In the multivariate logistic regression analysis of independent variables with p < 0.3 based on the post-hoc comparison of VM and MwVS, IWPH, aura, and comorbidity were significantly associated with VM (OR = 3.15, 95% CI = 1.15–8.6 and OR = 4.92, 95% CI = 1.75–13.8, respectively) (Table 4).

Table 4

Multivariate logistic regression model: VM-related factors in migraineurs with vestibular symptoms

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aura</td>
<td>4.92</td>
<td>1.15–8.6</td>
<td>0.025</td>
</tr>
<tr>
<td>IWPH</td>
<td>4.92</td>
<td>1.75–13.8</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Independent variables with p < 0.3 in the post-hoc univariate analysis were introduced in the model: aura, tinnitus, mechanical cutaneous allodynia, and IWPH. IWPH, interictal widespread pressure hyperalgesia; CI, confidence interval

The data supporting the findings of this research are presented in Additional File 2.

Discussion
Main findings

This study included 163 patients who were divided into the VM (19%), MwVS (33.1%), and MO (47.9%) groups. Significant differences were found in several variables, including aura frequency, osmophobia, tinnitus, acute CA prevalence, allodynia subtypes, TPC, and IWPH prevalence, between the groups. The prevalence of interictal CA was low and did not differ between the groups. Patients in the VM group had significantly higher TPC and IWPH prevalence than those in the MwVS and MO groups. Multivariate logistic regression analysis identified aura and IWPH as independent risk factors for VM in MwVS.

VM prevalence

In this study, vestibular symptoms were observed in 52.1% of migraine patients, consistent with the findings of previous research (51.7–61%) [46–48]. The prevalence of VM was 26.5%, which is higher than the rates before (9–12%) and after (10.3%) the new criteria were established, as reported in previous studies [1, 47, 49]. Calhoun et al. reported that nearly half of the participants experienced vertigo or dizziness when their headache intensity was 7 or higher, suggesting a strong correlation between migraines and subjective complaints of vertigo [50]. The high prevalence of VM in this study may be due to selection bias resulting from the study population and clinical context being limited to a secondary headache clinic.

Differences between VM and MwVS

VM has a higher frequency of migraine aura, TPC, and IWPH than MwVS According to multivariate logistic regression analysis, migraine aura and IWPH were independently associated with VM compared to MwVS.

In our previous study [24] of patients with both ictal and interictal migraine, no clinical differences were found between VM and MwVS except for the disability caused by possible criteria-selection bias. Thus, we believe that VM and MwVS may be on the same disease spectrum, which aligned with Abouzari et al.'s notion [25]. However, this hypothesis has been challenged in this study, which suggested different pathophysiology of aura and interictal hyperalgesia as the reason for the differences between VM and MwVS.

Female sex and VM

According to a previous report, VM predominantly affects females [7]; however, in the present study, no significant difference was noted in female sex between the three groups (Table 1).

The percentage of women in the VM, MwVS, and MO groups were 87%, 83%, and 72%, respectively. Although not significantly different at p < 0.05 (p = 0.123), this result potentially indicates a female dominance of VM and MwVS over MO. Further research with a larger sample size is needed to determine if this difference reaches statistical significance.

Aura and VM
The prevalence of migraine with aura in this study was 45.4%, which is considerably higher than that reported by previous studies (12–36%) [1, 47]. This difference may be attributed to selection bias resulting from our stroke clinic’s subspecialty. Symptoms of visual aura, such as temporary vision loss or changes, can be mistaken for transient ischemic attacks and are considered warning signs of a stroke. Therefore, many patients in Japan initially seek medical attention at a stroke clinic.

The association between vertigo and migraine with or without aura remains controversial. Some studies have reported a relationship between migraine with aura and vertigo [48], whereas others reported that patients with migraine without aura experienced vertigo more frequently [3, 47, 51–53].

A recent study that questioned the assumed relationship between dizziness/vertigo and migraine without aura showed that migraine with aura was significantly more associated with VM than with MwVS and MO [50]. Another study suggested that migraineurs that experienced aura are more likely to experience postural control impairments [54].

Our study found that vestibular symptoms are strongly associated with migraine with aura and not with migraine without aura. Logistic regression analysis confirmed that aura is closely related to VM, indicating the role of aura in the development of moderate-to-severe vestibular symptoms lasting for > 5 min, which is required for a vestibular migraine diagnosis.

Cutrer et al. proposed that short-duration vertiginous attacks lasting from a few minutes to 2 hours and associated with headaches are caused by the underlying mechanism, cortical spreading depression (CSD), as noted in other auras [55].

Demarquay et al. [56] proposed that vestibular aura (vertigo/dizziness) is a typical migraine aura resulting from transient parieto-insular vestibular cortex dysfunction caused by CSD. These symptoms may occur before or during headache attacks lasting between 5 min and 1 h, satisfying the vestibular symptom duration criteria for VM. Our study confirmed that VM was significantly associated with aura, but not with photophobia. This may be due to the role of the cuneus and lingual gyrus in photophobia [57], whereas a typical visual aura may originate from V3A [58].

**Headache intensity and VM**

Headache intensity did not differ significantly between the three groups, possibly due to the bias introduced by severe headache intensity of ≥ 7 criterion. The relationship between VM and headache intensity remains controversial, with some studies reporting no significant difference in headache intensity between VM and migraine without vertigo symptoms [59], whereas others report a strong correlation between headache intensity and vertigo [50].

**HIT-6 and VM**

In our previous study of 143 and 102 patients with interictal and ictal migraine, respectively, we found that VM can be effectively differentiated from MwVS and MO using the HIT-6 score [24]. Thus, we
recommended using the ICHD-IIIβ criteria for moderate or severe intensity with cutoffs range of 5 min to 72 h to identify severe cases of MwVS. However, we observed that this criterion was not effective in identifying patients with interictal migraine, possibly due to the small sample size.

**Osmophobia and VM**

The prevalence of osmophobia among 85 migraineurs with vestibular symptoms was 54.1% in the present study, which is similar to that reported by Akdal et al. [47, 48]. Osmophobia was significantly more prevalent in the VM group than in the MO group; however, photophobia and phonophobia did not differ significantly between the groups. VM had a significantly higher prevalence of osmophobia than MO in the present study, in contrast to the findings of previous studies [24] that found no significant difference. This difference may be due to differences in interictally sustained central sensitization. Osmophobia has been associated with allodynia [60], and further studies are needed to explore the relationship between interictal allodynia or interictal hyperalgesia and osmophobia.

**Tinnitus and VM**

Tinnitus was present in 45.2% of patients with VM in the present study, which is consistent with the results of prior studies [61–65]. Although the prevalence of tinnitus differed among the three groups, it was not significantly different between the VM and MwVS groups (p = 0.148, OR 2.84, 95% CI 1.00-8.34) based on post-hoc comparison and was included in the logistic regression model.

**Depression and VM**

Previous studies [24, 59, 65, 66] have reported differences in depression prevalence among the three groups, which was not replicated in this study, as shown by the lower prevalence of depression in the VM group (26%) than that in our previous report (34%) [24, 59, 65]. Interictal anxiety may be less severe than ictal anxiety, leading to lower SDS scores and less differentiation among the groups.

**Sleep disorders and VM**

In the present study, we found no significant difference in sleep disorder prevalence between the three groups, contradicting the results of prior research [24, 67, 68]. However, the prevalence of sleep disorders in VM and MwVS (19% and 20%, respectively) was twice as that of sleep disorders in MO (10%), suggesting potential disparities when larger sample sizes are used.

**Allodynia and VM**

Similar to the results of our previous study [24], significant differences were noted in the prevalence of acute CA (p = 0.026), extracephalic CA (p = 0.008), mechanical CA (p = 0.01), and widespread multimodal allodynia (p = 0.006) between the three groups in the present study. The prevalence of cephalic and thermal allodynia did not differ significantly. However, a noticeable trend was observed indicating a difference in the prevalence of cephalic allodynia between the three groups (p = 0.052).
Further investigation is required to determine if the reported discomfort associated with heat stimuli during headache attacks in the absence of headaches is susceptible to recall bias. Interictal allodynia has a low prevalence (14%), which was not significantly different between the groups. QST may be useful in evaluating interictal allodynia. Questionnaire-based investigation of widespread multimodal hyperalgesia [26] showed that VM and MwVS had equal thalamic sensitization, which was more than that of MO. Moreover, our evaluation of alldynia without headache suggested that VM and MwVS had equal central sensitization compared to MO. QST revealed the differences in the association of VM and MwVS with unaware CA, including acute and interictal CA [10, 13, 69].

**TPC and VM**

Post-hoc pairwise comparison revealed that VM had significantly higher TPC than MwVS or MO (Fig. 2), indicating that during the interictal phase, the pressure pain threshold (PPT) of VM is generally lower than that of MwVS and MO. As positive TP sites correspond to reduced PPT measured by QST, an increase in TPC suggests a widespread decrease in PPT [35, 70]. This finding suggests that TPC may differentiate VM from MwVS in migraine patients with vestibular symptoms.

[Figure 2 near here]

**IWPH and VM**

Post-hoc analysis revealed that IWPH was significantly more frequent in VM than in MwVS and MO (Fig. 3). Logistic regression analysis confirmed IWPH as a significant determinant of VM. These findings support the notion that IWPH plays a crucial role in the development of vestibular symptoms required for VM diagnosis. The pathophysiology of IWPH may involve impaired descending pain modulation [13], which can amplify headache stimuli in the thalamus and induce thalamic sensitization. This sensitized thalamus may give rise to a widespread multimodal CA, possibly due to dysregulation of the descending pain modulation [35]. Similar to the results of our previous study [24], no significant differences in CA subtypes were observed between VM and MwVS, including interictal CA. However, IWPH was significantly different between the two groups. This may be due to the suitability of hyperalgesia surveys compared to the recall-based allodynia questionnaires in detecting the differences in interictal asymptomatic persistent central sensitization or sub-allodynia [10, 13, 69]. As IWPH and acute CA were found to be correlated in our previous study [24], further investigation using QST during the headache-free phase may reveal differences in CA prevalence between VM and MwVS. The periaqueductal gray (PAG) descending control selectively modulates C and Aδ nociceptive input [38]. When compromised, amplified pain signals from the head, neck, and shoulders are transmitted to the thalamus via these fibers during headaches. Aβ fibers, which are not directly regulated by the descending system, transmit appropriate proprioceptive signals to the thalamus [71]. This may disrupt the spatial integration of pain and proprioceptive signals in the thalamus and cortex, leading to dizziness.

[Figure 3 near here]
Candidate origin of vertigo during migraine

Based on the above discussion, we assume that VM-related dizziness has four distinct origins: 1) peripheral vertigo, which is related to the Meniere's disease-like inner ear disorders [72]; 2) subcortical vertigo, which is related to the modulation of vestibular input by the sensitized thalamus [24]; 3) cortical vertigo, which may be a possible focal symptom due to CSD [56]; and 4) vertigo due to impaired descending modulatory system, leading to disturbed perception integration in the thalamus and cortex.

IWPH as a potential clinical marker to distinguish the interictal phase of VM and MwVS

The questionnaire survey findings indicated that interictal allodynia was not significantly different between VM and MwVS during persistent central sensitization. However, a TPC survey revealed a significant distinction in the prevalence of IWPH between VM and MwVS, indicating the existence of asymptomatic central sensitization that persists into the interictal phase. IWPH could be a valuable clinical marker for differentiating between VM and MwVS.

Strengths and limitations

The strengths of this study include well-defined migraine status, detailed information on associated symptoms, and standardized semi-quantitative assessment of IWPH. IWPH's prevalence, an objective finding linked to central sensitization or pain control system impairment, was practically and reproducibly investigated using MTPS and not QST. Most importantly, this is the first study to demonstrate that aura and IWPH are independent factors, which were significantly associated with VM compared with MwVS, and can be used to distinguish between the two. By focusing on migraine patients between headache attacks, the study identified clinical features that differentiate between VM and MwVS. The study results enhance the understanding of VM. However, our study has some limitations: First, recruitment from a headache clinic may have introduced sample bias toward moderate-to-intense headaches and moderate-to-less intense dizziness, limiting the generalizability of our findings. Second, using a headache questionnaire may be subject to recall bias for allodynia and vestibular symptoms. Third, the lack of multiple IWPH raters may affect inter-rater reliability. Finally, our cross-sectional design only described symptom association, precluding firm conclusions about potential causality between aura and VM or between IWPH and VM.

Generalization of the findings

The factors associated with VM in this study can be applied only to patients who visit headache clinics and not the general population. The demographic and clinical features of migraine, including the prevalence of vestibular symptoms, were consistent with the findings of previous studies performed in several countries.
Directions for future research

Further research is needed to replicate this study’s findings in diverse populations to determine the relationship between vestibular symptoms, allodynia, and hyperalgesia using QST in collaboration with clinical examinations by ear, nose, and throat specialists. These clinical examination results may contribute to the understanding of the pathophysiology of VM through central sensitization. Determining whether VM symptoms protect against migraine-related hypersensitivity is crucial, given recent reports of vestibular signals modulation of nociceptive processes in the somatosensory cortex [71].

Conclusions

The cross-sectional study analyzed the clinical characteristics, including IWPH as a potential indicator of persistent central sensitization, among VM, MwVS, and MO in 163 interictal migraine patients. The multivariate logistic regression analysis highlighted aura and IWPH as independent predictors of VM. Despite no significant interictal differences between MwVS and MO, VM displayed a unique pathophysiology characterized by aura-related mechanisms and persistent central sensitization, notably IWPH. Importantly, these findings could improve our understanding of these migraine variants, potentially influencing management strategies and aiding in the development of more effective, targeted treatments.

Abbreviations

CA
Cutaneous allodynia
CI
confidence interval
HIT
headache impact test
IWPH
Interictal widespread pressure hyperalgesia
ICHD
International Classification of Headache Disorders
MO
Migraine only
MTPS
Manual tender point survey
MwVS
Migraine with vestibular symptoms not meeting vestibular migraine criteria
NRS
numerical rating scale
OR
Odds ratio
Declarations

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

Consent for publication: Not applicable.

Availability of data and materials: All data generated or analysed during this study are included in this published article and its supplementary information files.

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Authors’ contributions: TT wrote the initial draft, YH made significant revisions, and all authors contributed to the final revision. TH supervised the study planning. All authors read and approved the final manuscript.

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References


Figures
Figure 1

Flow chart of patient selection. MO, migraine without vestibular symptoms; MwVS, migraine with vestibular symptoms not meeting the vestibular migraine criteria; VM, vestibular migraine.
Figure 2

Box plot comparison of tender point counts among VM, MwVS, and MO Groups. MO, migraine without vestibular symptoms; MwVS, migraine with vestibular symptoms not meeting the vestibular migraine criteria; VM, vestibular migraine.
Figure 3

Comparison of IWPH frequency differences Among VM, MwVS, and MO Groups. MO, migraine without vestibular symptoms; MwVS, migraine with vestibular symptoms not meeting the vestibular migraine criteria; VM, vestibular migraine.

Supplementary Files

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