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UNIVERSITY OF CALIFORNIA, IRVINE

Vestibular Migraine and the Overlapping Features Observed in those not Meeting Diagnostic Criteria

THESIS

Submitted in partial satisfaction of the requirements For the degree, of

MASTER OF SCIENCE

In Biomedical and Translational Science

Ву

Omid Moshtaghi

Thesis Committee: Professor Hamid R. Djalilian, Chair Assistant Professor Harrison W. Lin Associate Professor Sunil P. Verma Professor Sheldon Greenfield

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Dedication

This work is dedicated to my supporting wife, who has been with me every step of the way.

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Abstract of the thesis

Vestibular Migraine and the Overlapping Features Observed in those not Meeting Diagnostic Criteria

By Omid Moshtaghi

Master of Science in Biomedical and Translational Science University of California, Irvine, 2017

Dr. Hamid R. Djalilian, Chair

Background: For the first time in 2013, the international classification of headache disorders

(ICHD) published a diagnostic criterion for vestibular migraine (VM). This provided, legitimacy to

a diagnosis previously rejected by many, further driving a discussion regarding its validity.

Objective: To characterize a cohort of patients suspected of having VM.

Methods: Spanning a 3-year period, questionnaires were provided to patients at an outpatient neurotology clinic assessing ICHD diagnostic criteria for VM, and migraine.

Results: Of the 396 participants included, 26% met criteria for VM, 25% met criteria for migraine only with no VM (MO), and 48% met no criteria (MNC) for either migraine or VM. Significant overlap in vertigo symptoms was observed in the MO group compared to VM participants, with only 3 of 11 features proving to be statistically different between the two. Similarly, 21 of 23 features of migraine were equivalent between the MO and VM group. In contrast, MNC and VM groups were significantly different in almost all features relating to migraine, vertigo and quality of life.

Conclusions: Evidence of the significant symptomatic overlap observed in VM and MO groups demonstrates the two could be suffering from an identical disease process. In addition, the

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MNC group may belong to a benign recurrent vertigo entity due to a lack of features necessary to achieve ICHD criteria for migraine or VM. In all cases, there is evidence that migraine may play a significant role in vertigo symptoms, leading to a possible therapeutic improvement with migraine prophylaxis.

Introduction

Vertigo is the perception of self-motion when no self-motion is occurring, ¹ and can have etiologies that lie in the CNS or peripheral vestibular system. In contrast to other otolaryngological diseases such as tumors and nerve paralysis, no definitive diagnostic test exists to confirm the presence of vertigo. Instead, its evaluation is based almost entirely on patient history making it a clinical diagnosis.

Vertigo in aggregate with migraine is a common complaint and cited as one of the top ten most common reasons for a neurological exam. ² The co-occurrence of these diseases has a unique impact on patient quality of life effecting both social and lifestyle productivity. ³ The combination of migraine features and vertigo has been referred to as vestibular migraine (VM).

Although VM has been described in literature for centuries, only recently has there been efforts to classify this disorder. Publications on the topic has increased in that past 15 years with only 9 PubMed publications for the year 2000, which rose to 68 by the conclusion of 2016. Similarly, our research team has also recognized the overlapping symptoms of those presenting with migraine and vertigo. We became familiar with a repeating cohort of patients presenting with a chief complaint of vertigo with no mention of migraine. Upon further investigation and only when prompted during the patient interview we recognized significant migraine features in a large majority of this population. Patients commonly endorsed vertigo triggers related to periods of starvation, or sleep deprivation, analogous to the common triggers of migraine. ^{4,5} Coupled with the knowledge that the majority migraine suffers go undiagnosed ^{6,7} we attempted to expanding upon this topic in literature and collect data on those presenting with VM characteristics.

Subsequent to these observations, beginning in 2012 the research team began treating this specific patient population with migraine medications independent of criteria described in literature. Upon review of our practice methodology, most patients did not meet criteria for VM according to the widely accepted international classification of headache disorders (ICHD) criteria, yet each patient provided a history highly suggestive of migraine and was thus considered to have vertigo relating to migraine. Our observations are similar to other authors who recognized the strong clinical correlation between migraine history and vertigo events.⁸⁻¹² Authors report that only a minority of these patients meet ICHD criteria for migraine or VM. Instead, diagnosis was confirmed with migraine prophylactic medications, rehabilitation or lifestyle changes. As a result, significant symptomatic improvement in vertigo symptoms was documented among many. Although these studies predate ICHD VM criteria, each patient was diagnosed according to the clinician's assessment and suspicion of migraine. In an analogous selection manner, patients suspected of VM were prescribed migraine prophylaxis and lifestyle changes. Although beyond the scope of this thesis, we observed clinical success in nearly all patients responding to medication therapy, the majority of which achieved complete symptomatic improvement.

Objective

With ICHD criteria relatively recent publication in 2013, few studies have applied the criteria to a large patient cohort. Although all patients included are highly suspected of having VM, we hypothesize that most will not meet official ICHD criteria for VM yet will have overlapping features. We thus set out to better understand the population not meeting criteria

and describe its similarities and differences in symptoms. As such, our aim is to achieve three objectives: 1) describe a large cohort of VM patients defined by ICHD, 2) compare a diagnosed migraine population experiencing vertigo against those with VM, 3) describe a population that does not meet any diagnostic criteria of migraine or VM yet has significant migraine and vertigo history.

Background

The first accounts of migraine occurring in the context of vertigo was described in 100 AD as described in the work of Areteaus of Cappadocia. ¹³ Later, vertigo and migraine was described in the 1800 by Prosper Meniere when describing his name sake disease. ¹⁴ By 1917, Boenheim first coined the disorder as "vestibular migraine." ¹⁵

The link between vertigo and migraine became firmly established in the landmark report in 1984 by Kayan and Hood. ¹⁶ As the symptomatology pattern of migraine with vertigo evolved in 1992 Cutrer and Baloh began using the term "migraine- associated diseased." ¹⁷ In 1997 the term changed to "migraine associated vertigo" and was finally identified as an independent diagnostic entity. ¹⁸ Eventually, the accepted term reverted back to "vestibular migraine" originally coined in 1917.

Prevalence

In those suffering from migraine, vertigo has been shown to have a prevalence of 24%-27%. ^{16,19} Accordingly, those with migraine have a high prevalence of vertigo with 30-61% of migraine patients also suffering from vertigo. ^{18,20,21} Some suggest these observations are a mere coincidence with migraine and vertigo each have a high prevalence in the general population of 14% and 7% respectively. ^{22,23} Yet, the 1% probability of the two occurring together by chance alone makes it unlikely. Similarly, one study determined this chance to be 3.2%.²⁴

In studies describing VM using various criteria its prevalence is thought to occur in 4.7%-29% of vertigo patients presenting to an otolaryngology clinics specializing in imbalance. ²⁵⁻²⁷ Its

ubiquitous finding is thought to be the second most common cause of vertigo second only to benign positional vertigo (BPV)^{26,28}

Differential Diagnosis of VM

A patient presenting with vertigo can be difficult to treat by any specialist in the field, having a broad differential diagnosis. Despite the common occurrence of VM, other etiologies of vertigo in the context of migraine must be ruled out before the diagnosis can be confirmed. This includes episodic ataxia, transient ischemic attacks, somatoform vertigo, orthostatic hypotension, and psychiatric dizziness.²⁹⁻³² The most challenging diagnostic feature of VM is differentiating it from Meniere's disease (MD). Both present with similar duration and severity of vertigo.³³ In addition, the cochlear symptoms of tinnitus, ear fullness and hearing loss of Meniere and VM exhibit significant overlap ³⁴⁻³⁶ As a result, it is thought by some that Meniere and VM show enough overlap to be considered the same syndrome.^{37,38}

Defining the Diagnostic Criteria

Although the phenomena of VM has been described for century's, in 2001 the first formalized criteria was proposed by Neuhauser. ²⁶ Subsequent to its publication, multiple versions of VM criteria was developed over the next decade with definitions continuing to evolve. ^{35,39-42} Despite the criteria described by many, the international classification of headache disorders (ICHD) is the most widely recognized entity used to describe migraine. In previous versions of ICHD guidelines, VM was not recognized. ⁴³ Instead, the only reference to

vertigo in the context of migraine was basilar type migraine under the classification of migraine with aura.

After much deliberation and extensive review on the topic, in 2013 VM was officially accepted by the ICHD 3rd edition beta. ⁴⁰ In this version, descriptions of three different types of migraine were included: migraine without aura, migraine with aura and VM. The 3rd edition beta version took three years to develop and was created in partnership with the world health organization (WHO) to create ICD codes that would could be used internationally for all defined headache sub-groups. ⁴⁴ It's classification as a beta version was at the WHO request so it can be field tested for 2 to 3 years with only small changes anticipated to take place before its finalized publication.

Despite the recent recognition of VM by ICHD, authors continue to use other diagnostic criteria bringing into question its accuracy and utility. One group in particular used ICHD to diagnose VM yet also treated those not meeting criteria but thought to have VM according to clinical history. ⁴⁵ Findings show significant vertigo relief with migraine prophylaxis in all groups experiencing an equal symptomatic improvement regardless of diagnostic criteria. This practice is echoed in another group diagnosing VM patients according to either Neuhauser or ICHD criteria. Similarly, those that did not meet any criteria but had a significant personal or family history of migraine as determined by the clinician were still included in the study. ⁴⁶ As a result, all patients achieved statistically significant improvement regardless of diagnostic classification. Furthermore, randomized clinical trials continue under the diagnostic definition outlined by Neuhauser with no reference to ICHD. ⁴⁷ Others chose to use both Neuhauser and ICHD criteria when defining VM populations to determine inclusion criteria. ^{25,27} A further lack of agreement

in defining VM is seen in studies using Lampert criteria for defining and treating eligibility in a randomized control drug trial and observational studies, not ICHD. ^{48,49} In contrast many authors have accepted and applied its criteria to their research population. ⁵⁰⁻⁵⁴ Yet, unanimous consensus for one criteria does not currently exist to date.

Lack of Consensus

Although VM has been written about for decades, it has been slow to gain acceptance, citing the overlap between migraine and vertigo to be a consequence of coincidence. Furthermore, acceptance within the different fields has varied. A considerable lack of consensus regarding the role migraine plays in vertigo has been demonstrated when surveying practitioners belonging to different specialties. This is evident in surveys collected from neurotologists belonging to the American Neurotology society and ICHD members composed mostly of neurologists. ⁵⁵ When surveyed, only 9% of neurotologists believe VM is of trigeminal origin compared to the 60% of neurologist. Even among those who accept VM, inconsistency in treatment was noted. Neurologists were more likely to prescribe anticonvulsants while neurotologists utilized antidepressants and beta blockers.

The lack of agreement on this topic is troubling, with patients who have seemingly identical pathologies receiving different treatments depending on the specialist they encounter. Some suggest this observation is due to a significant lack of knowledge that exists among clinicians resulting in a failure to recognize these findings.⁵⁵ This has led to a considerable underdiagnoses of VM.⁵⁶ Others such as, Philips et al. have reject the concept of vestibular migraine as an entity in itself.⁵⁷ This group suggests that VM is a result of an inaccurate

characterization of vertigo that has been confused with anxiety disorders associated with migraine and vertigo. The recent acceptance if VM according to ICHD criteria in 2013 makes this hypothesis less likely and has provided more legitimacy to this diagnosis.

Study Rational

With the new guidelines established by ICHD, relatively few studies have characterized and described the criteria in a large cohort of the population. Furthermore, few have characterized those not meeting VM criteria and commented on the overlapping symptoms. Thus, very little is known about those suspected of VM yet not meeting criteria according to ICHD especially its relationship to migraine. This study sheds light on the overlap of symptoms between those that do not meet VM criteria, suggesting that ICHD may not be accurately identifying all possible patients.

Methods

From January of 2014 to 2017 questionnaires were administered to patients presenting with a chief complaint of vertigo at an outpatient neurotology clinic at a tertiary care academic center. Permission was obtained prior to data collection from our internal institutional review board. Inclusion criteria for participation in the study was having a substantial history of migraine in conjunction with chronic and episodic vertigo. Those meeting the following criteria were excluded: 1) new onset vertigo lasting less than four weeks 2) constant and persistent vertigo with no relief, suggesting a tumor etiology. Eligibility was determined during clinical exam and history obtained by the treating physician. All patients enrolled were initiated on a migraine prophylactic regimen given at escalating doses. In addition, all were instructed to practice consistent sleep hygiene and adhere to a strict migraine diet which includes avoidance of foods known to trigger migraines.

Questionnaire

Primary outcomes of the questionnaire included classifying patients meeting ICHD 3rd edition beta criteria for definite VM, probable VM, migraine without aura and migraine with aura **(Table 1)**. ⁴⁰ Secondary outcomes were characterizing migraine and vertigo symptoms described by patients to define any possible symptomatic overlap. Those meeting migraine criteria with or without aura but not VM were designated as the migraine only (MO) group. Those meeting neither criteria for VM or migraine were considered an independent entity and designated to the meet no criteria (MNC) group.

Because VM and migraine is a clinical diagnosis determined by patient history, our survey was designed to capture this data in a reliable and reproducible manner. Others have used a variety methods for screening including structured interview, and questionnaire. ^{24,58,59} After careful consideration, and in attempt to provide minimal disruption to clinic workflow, our team elected to adopt a paper questionnaire for the study at hand.

The questionnaire was composed of three parts. The first provided a qualitative and quantitative evaluation of migraine and vertigo episodes, severity, triggers, and associated symptoms in order to determine a diagnosis of VM and migraine. This portion was developed by the research team to identify which patients meet ICHD criteria. The second portion quantified how vertigo affects quality of life (QOL). The instrument used was modified from an existing Meniere's disease dizziness outcome questionnaire. ⁶⁰ The questionnaire was modified for our patient cohort to assess the impact of vertigo on QOL over a preceding two-month time frame. The questionnaire was composed of 18 multiple-choice questions with a maximum possible score of 72. The instrument measured QOL globally in addition to 3 domains: physical, emotional, and social well-being. The third section used the widely cited perceived stress scale to measure the amount of stress experienced by each participant. ⁶¹ The value of 13 was considered to be an average score.

Defining Vertigo Triggers and Characteristics

A wide variety of vertigo triggers and characteristics was recognized by participants. As such, our team followed definitions according Neuhauser to better classify the type of vertigo experienced. ³ Positional vertigo trigger was defined as vertigo or dizziness precipitated by

changes in head position such as lying down or turning in bed. Triggers of visual motion was defined as vertigo experiencing as a passenger in a car, or watching a 2 or 3-dimensional movie. In some cases, patients described multiple types of triggers qualifying them for both categories.

Statistical Analysis

Statistical analysis was performed using PASW Statistics 18.0 software (SPSS Inc, Chicago, IL) with an alpha less than 0.05 considered to be statistically significant. Descriptive statistics was used to determine the association of migraine diagnosis and other independent variables. Two independent analysis were completed comparing MNC and MO groups to those with VM. Fisher's exact test and independent samples t-test was used to compare dichotomous and categorical variables respectively. Although the use of Bonferroni corrections may have been statistically valid, lowering the alpha level could have masked critical differences between the two group comparisons. Thus, we chose to maintain a high threshold for statistical significance to ensure no type I errors were made.

Results

Diagnostic and Demographic Composition

A total of 396 survey questionnaire responses were included in this study. The average age of all subjects enrolled was 53 years old (range: 14-81). Those that MNC were noted to be significantly younger than the VM group **(Table 2)**. A strong preponderance of females was observed composing 66% of study participants. Across all three groups, no difference in gender was noted.

A total of 104 (26%) met criteria for VM. Within this group, 91 (88%) experienced migraine with aura while 13 (12%) had migraine without aura. No VM patient experienced isolated VM in the absence of migraine with or without aura. A total of 100 (25%) participants was given the designation of migraine only (MO) with no VM. Within this group, 91 (91%) met criteria for migraine with aura and only 9 (9%) suffered from migraines without aura. The remaining participants that met no criteria (MNC) totaled 192, composing 48% of the participants. Furthermore, it was determined that of the 100 in the MO group, 42 (42%) meet criteria for probable VM. Of the 192 that MNC, 30 (15%) met criteria for probable VM.

Vertigo history

On average, patients reported two vertigo episodes per day initially beginning 7 years prior to clinic presentation **(Table 3)**. Age at first vertigo symptoms was 46 years old. Irrespective of diagnosis, 322 (81%) reported migraine accompanying vertigo. The most frequent type of dizziness was determined to be positional vertigo observed in 324 (82%) of

patients. The most common cochlear complaint associated with vertiginous episodes was tinnitus 227 (57%), ear pressure 220 (55%), and hearing loss 157 (40%).

When comparing symptoms between the VM and MNC group 5 of the 11 features proved to be statistically different. These symptoms include age at first vertigo episode, vertigo accompanied by migraine, rotational vertigo rates, vertigo triggered by visual motion rates and tinnitus. In contrast, when comparing VM and MO groups, only 3 of 11 features proved to be different which was age at first vertigo trigger, duration of vertigo, and dizziness accompanied by migraine.

Migraine history

A total of 322 (81%) patients in this study reported a personal history of migraine headache, reporting it to occur four times per week with the first symptoms initially beginning 14 years prior to clinic visit. Age of first reported migraine headache in all patients was 36 years old. Across all groups no difference was observed in age of first migraine episode, migraine frequency, sinus headache and unilateral findings **(Table 4)**. A difference in personal and family history of migraine was observed both in MO and MNC groups when compared to VM.

The most common migraine symptom was light and sound sensitivity, reported by 49% and 48% of participants respectively. MNC group reported lower rates of all headache symptoms showing a statistically significant difference across all migraine symptoms. In contrast, no difference in migraine symptoms was noted in the MO group compared to VM.

Among all participants, sleep disturbance was the most common trigger, observed in 52% of participants. Of the 261 women, 122 (46%) determined menstruation as a trigger for

migraines. For MNC group, the rates of migraine triggers were determined to be statistically different, exhibiting lower rates of migraine triggers compared to VM patients. Yet no difference was noted when comparing the findings to the MO group.

Quality of life and stress

Overall, patients reported an average global QOL score of three out of five indicating that dizziness affects overall life "moderately." Upon further analysis of the mental, physical and social domains, average scores corresponded to 3.2, 2.9, and 3.3 respectively. For the MNC group, all quality of life measures was statistically different than those with VM except for the physical domain **(Table 5)**. Correspondingly, the MO group was different only in regard to social and global QOL.

The average PSS score among the cohort was 16, with average scores corresponding to a value of 13. Those of MNC group were statistically different than the VM group, but was the same in the MO group.

Discussion

Comparisons of symptoms confirms our hypothesis that the MO group is nearly identical to the VM group. With notable exceptions, the two groups have a similar demographic composition, vertigo history, migraine history, quality of life and perceived stress. Because VM is a clinical diagnosis, the significant symptomatic overlap between MO and VM suggests both may be the same disease process. In contrast, the MNC was statistically different in nearly all descriptive qualities.

The VM population we have described is similar to other populations in previous studies. Like others, we observed a significant female preponderance. ^{9,17,35,62,63} Vertigo symptoms occurred on average 5 years after migraine onset, a consistent phenomenon observed in other studies as well. ^{26,35,54} Notable differences was our population had an older age of migraine onset of 36 as compared to other studies taking place in Germany and China having an average age of 20 and 32 years old respectively. ^{54,63}

Although ICHD outlines a diagnosis of probable VM, only 42% and 15% of those within the MO and MNC respectively meet criteria. This leaves an incomplete number of subjects in the population not meeting classification. One randomized clinical trial treated VM, probable VM, and those that meet no diagnostic criteria and determined no differences in efficacy across the three groups. ⁴⁵ This suggests that even a probable diagnosis of VM may be limited diagnostically.

In many cases, having a probable diagnosis of VM does not provide enough confidence to change clinical management or define inclusion criteria for a target research population. Of the recent studies used to characterize VM after ICHD publication, 3 did not take into account

probable VM, ⁵²⁻⁵⁴ while four did account for probable VM ^{45,50,51,64} Thus, the role that probable VM plays is in literature is questionable with its clinical role even more unknown.

Similarities in the VM and MO Group

Although confounding variables may explain the similarities in VM and MO groups, the demographic composition of the two groups are comparable with no difference observed in age or sex. In addition, nearly every other metric used to describe the two groups showed little difference. Notably, the type of vertigo symptoms and its triggers were the same.

Positional vertigo is common feature in VM as documented by many. Positional vertigo is feature that was similar among both groups and was seen in 88% and 83% of those with VM and MO respectively. These rates are higher than the 40% to 70% documented in VM patients using alternative diagnostic criteria. ^{16,65,66} Yet recent publications using ICHD VM criteria, applying our definition of positional vertigo report rates similarly to be 43%-73%. ^{54,67} With the consistently common rates of positional vertigo seen by others and our study it is clear that this is an important descriptive symptom of true VM patients. With 83% of our MO group displaying similarly high rates for this type of trigger, it provides further evidence of the symptomatic similarities displayed by VM patients.

Visual vertigo is another unique and characteristic feature of VM. It is defined as vertigo triggered by visual motion such as 3 dimensional movies, or as a passenger in a car. This feature has been well documented in VM studies using alternative VM criteria. ^{11,62,68,69} In contrast, studies applying ICHD criteria determined visual induced vertigo to be present in 0-13% of VM patients. ^{54,67} Our findings are inconsistent with these reports, with evidence of visual vertigo

seen in 78% and 72% of our VM and MO population respectively. It is unclear why this may be the case, but visual vertigo is closely correlated with migraine and has been shown to occur between 25-54% of an unselected migraine population. ^{16,26} This shows that the MO group may indeed be suffering from vertigo relating to a migraine process. The correspondingly concordant high rate of visual vertigo observed in the MO and VM population is another indication of the overlap of symptoms in these two diagnoses.

Differences in the VM and MO Group

When comparing VM and isolated migraine not all features were identical with key differences noted. Of importance, a difference was noted in those endorsing vertigo and migraine headache symptoms co-occurring together. Our data shows 87% of those with VM experienced vertigo during migraine attacks. This finding is consistent with recent studies using ICHD criteria, that report nearly all VM patients described experience VM and migraine concurrently. ^{54,67} Yet, previous studies using different diagnostic criteria for VM have reported a lower association reporting the two occurring simultaneously 24%-45% of the time. ^{16,24,26,66,70} Similarly, in our cohort of MO, 63% experienced migraine during vertigo, well above rates used to describe VM according to non-ICHD diagnostic criteria.

Current ICHD criteria suggests that vertigo episodes should be closely related to migraine as demonstrated in our VM group. Yet, almost one third of our MO cohort did not experience vertigo and migraine concurrently- excluding many from meeting VM criteria. Others have commented on the underdiagnoses of VM when vestibular symptoms occur independent of migraine headache, posing a critical challenge for clinicians. ^{9,71-73} Thus, ICHD

criteria could be excluding a significant proportion of possible VM patients experiencing vertigo and migraine headache separately.

Another notable difference between the two groups is VM patients experience longer vertigo episodes compared to those with MO. Patients suffering from MO experienced dizziness on average for 84 hours compared to the 11 hours in the VM group. This factor is an additional defining factor for why those with migraine may not have fit criteria for VM. ICHD criteria precludes a VM diagnosis if dizziness symptoms last longer than 72 hours but is shorter than 5 minutes. Despite the significant overlap in migraine and vertigo symptoms in our cohort of MO, 40 of 100 (40%) were disqualified from VM criteria due to the duration of vertigo. It was noted that 23 (23%) experienced dizziness for less than 5 minutes and 17 (17%) experienced dizziness beyond 72 hours.

In characterizing vertigo duration in VM, other authors have used a variety of time frames. According to Neuhauser criteria, 18% of the VM patient cohort experienced vertigo lasting less than five minutes. ²⁶ In addition, a prominent study used to assess VM according to ICHD authors chose to exclude the criteria of 5 minutes to 72 hours when clinicians felt it was appropriate. ⁵⁴ The duration of vertigo is meant to rule out both brief vertigo caused by other etiologies such as BPV and long lasting vertigo caused by central mechanisms. But reports in literature and our findings bring into question the proper time frame.

Two different mechanisms of action can explain the duration of vertigo caused by migraine. Short duration vertigo spanning minutes to hours may result from the same mechanism of cortical depression observed in migraine with aura. ¹⁷ Longer lasting episodes beyond 24 hours alternatively can be caused by neuroactive peptides. ¹⁷ Calcitonin gene related

peptide (CRGP) create a more characteristic headache phase of migraine rather than the shortlived aura symptoms. Furthermore, vertigo symptoms lasting beyond 72 hours may have a similar pathophysiology of status migranosus. In status migranosus, patients experience a migraine headache lasting more than 72 hours. ⁷⁴ Those experiencing vertigo during the same time frame can also be suffering from an episode of status migranosus manifesting as vertigo symptoms. Thus, arguments can be made that limiting a VM diagnosis to vertigo lasting within a 5 minute and 72-hour time window excludes many patients possibly suffering from VM.

Alternatively, it is possible to consider ICHD criteria for vertigo duration as accurate yet erroneously reported by the patient. Patients could be experiencing true vertigo lasting between 5 minutes and 72 hours, yet feel unsteady for days and weeks after. When asked about the duration of vertigo, patients many may mistakenly state the duration of feeling imbalance, not true vertigo. In either case, the true duration of vertigo will be unknown to the clinician as reported by the patient, placing a restrictive duration criteria for VM.

Pathophysiologic Explanation Linking MO to VM

The significant overlap existing between VM and MO groups, may be evident not only on a symptomatic level but pathophysiologic manifestations as well. Using a MRI technique of voxel based morphometry there is evidence of a radiographic justification for the overlap. A similar pattern of gray matter volume reduction was found in those with migraine and VM.⁷⁵ Those with VM were found to be identical expect for an expansion into areas of the brain involved in vestibular control. The link between VM and migraine is also demonstrated in genetic linkage mapping displaying inheritance patters.⁷⁶ Wide genome mapping resulted in

identifying a specific locus for familial VM, with a strong prevalence of migraine in those with the gene. ⁷⁷ Physical manifestation of vertigo is also evident in those with migraine. As expected, VM patients were twice as likely to exhibit abnormalities on vestibular testing. Yet those with migraine and no vertigo also displayed significant abnormalities. With authors suggesting the existence of a subclinical vestibular dysfunction in all with migraines. ⁷⁸ Others have shown similar results in VM patients defined by ICHD. ⁷⁹

Each of these findings suggests a pathophysiological link on an anatomic, genetic and physical association between those with MO and VM. Therefore, drawing a clinical distinction between the two could be artificial in that the pathophysiologic mechanisms may be closely related.

Characterizing the MNC Group

A substantial portion (48%) of our cohort suspected of VM did not meet ICHD criteria for migraine or VM. Yet, 32 (16%) of these patients did meet criteria for probable VM as previously discussed which may be of limited clinical significance. Others have similarly observed a subset of vertigo patients with no diagnosis and described these patients as "not otherwise specified." An equivalent term used is benign recurrent vertigo (BRV). ⁴¹ No official diagnosis exits for BRV, with a broad range of definitions used by many authors.

Slater was the first to described BRV in 1979 using a methodology similar to that described in this manuscript. He applied criteria to a patient cohort with vertigo that did not meet diagnostic criteria for migraine but suffered from migraine or had a family history of migraine. ⁸⁰ Slater's observations led him to conclude that BRV could possibly be a migraine

equivalent. This has been reinforced by modern studies using various definitions of BRV showing evidence for the strong link to migraine headaches. ^{9,16,17,21,33,62,80-84}

Current literature uses a variety of definitions to describe BRV- some exclude vertigo triggered by head movements, others exclude those with history of migraine. ^{84,85} One thing is clear, is no strict definition of BRV exits, and current ICHD criteria does not recognize BRV as a migraine equivalent. ⁴⁰ Instead, it is a term loosely applied to those with no other etiology of vertigo- specifically having Meniere's disease ruled out.

Although commonly occurring together, the relationship between migraine and BRV is not absolute. One study determined that half of BRV patients did not subsequently meet criteria for migraine according to ICHD. ³³ Similarly, we determined 33% of our BRV patients have not experienced migraine headache. Although, of those reporting no history of migraine, 17% report a family history of migraine. Studies show that both migraine and BRV display a heritable pattern. ^{65,86} In this cohort, although some may not experience classic migraine headache they could be experiencing a migraine manifestation of vertigo passed on genetically. Furthermore, 28% of those not endorsing migraine headaches report a history of chronic sinus headache which is strongly linked to migraine. Research has shown that sinus headache is a migraine equivalent due to the overlapping features and evidence of improvement with migraine medications. ^{87,88}

By taking into account family history and sinus headache, this this leaves only 19% of our entire BRV cohort with no detectable migraine history. For the remainder of the cohortclear personal, family and symptomatic presence of migraine existed. Thus, when compared to a previous study describing BRV, our cohort of those who MNC may similarly be described as

BRV. ⁸⁴ Because BRV is a diagnosis of exclusion, using VM criteria established by ICHD, patients originally thought to have BRV in the past would met current VM criteria today. Therefore, this thesis is the first to offer an accurate description of a true BRV population with VM and migraine with those defined by ICHD excluded. By firmly establishing the relationship of migraine and BRV, the next reasonable step would be to treat this patient cohort with migraine prophylaxis. To date, no study has treated this population to confirm the role migraine plays in BRV.

Need to Expand Criteria

With similarities demonstrated between the two groups which do not meet VM criteria, arguments could be made that current ICHD criteria are too stringent. As a result, diagnosis is highly specific at the cost of low sensitivity, excluding a significant portion of patients who could be suffering from VM. The possibility exists that those who do not meet VM criteria could be experiencing migraine and vertigo by chance and are thus unrelated. Yet, this is unlikely to be the case due to the improvement in vertigo after initiating migraine prophylaxis reported by others. ⁸⁻¹¹

In our study, only a fraction of our patients suspected of VM met ICHD criteria. When ICHD criteria is applied retrospectively to published studies describing VM, 30-50% of patients do not meet criteria for VM as well. ^{24,26,35,63} In a time when ICHD criteria did not include a diagnosis of VM, Neuhauser developed his own criteria which continues to evolve and be modified throughout the decade. ²⁶ Now in an era where VM is recognized by ICHD, we similarly propose continued modification and expansion. Expanding criteria has important

clinical significance. Clinicians of all specialties are guided by evidence based practices and treat patients if symptoms fulfill diagnostic criteria. Thus, a patient suffering from VM but not fulfilling ICHD criteria may not receive appropriate treatment due to a possibly stringent guideline. Therefore, we propose an expansion of current VM criteria and allow patients with a substantial history of migraine to benefit from prophylactic therapy.

Future Directions

To our knowledge, no definitive molecular or diagnostic test exists to confirm the diagnosis of VM. Future studies must use response to migraine prophylaxis as the gold standard to confirm VM. In identifying patients who respond to medication and working retrospectively to identify commonalities, more accurate and inclusive criteria to VM can be developed.

Our group has taken a similar approach to migraine related vertigo in Meniere's disease and mal de debarquement syndrome. ^{38,89} Only with detailed history and maintaining a high index of suspicion for migraine can these clinical findings be observed. In our practice, migraine diaries have been essential in maintaining the accuracy of our diagnosis, and have proven its efficacy in previous studies. ^{90,91} This practice however has not been utilized in the context of vestibular migraine in which multiple triggers and complex factors could be at play. Furthermore, attempts at characterizing these patients with molecular testing should be made. For example, CRGP has long been known to be prevalent in migraine patients. ⁹² Thus, this testing should be performed in a large cohort of VM patients to show a definitive connection of migraine in these patients meeting no diagnostic criteria.

Limitations

The patient population described is a highly selected population at a tertiary academic intuition with a suspicion of VM, introducing a significant selection bias. Recall bias may also play a role, with most patients enrolled suffering chronic migraine and vertigo symptoms extending over long periods of time. Under these conditions it could be difficult to accurately recall symptoms and triggers. In addition, response bias may also be at play in the description of symptoms. Each patient was expected to choose from a list of many choices leaving a high likely hood of erroneously choosing symptoms that could not be relevant. It has been shown that patient description of dizziness symptoms using conventional questionnaires may be flawed, producing inconsistent and unreliable results.⁹³ In turn, we have attempted to mitigate this possibility by developing a questionnaire in which patients are asked multiple questions and have an opportunity address a variety of options.

Furthermore, this study did not include a control group. A group suffering from vertigo but having no migraine features would have served as a reference cohort to provide more evidence in support of the findings in our study. Future studies should account for these confounding factors before definitive conclusions can be applied to the general population.

Conclusion

With the release of new ICHD criteria for VM in 2013, this topic has been of great interest for researchers and clinicians alike. As such, few studies have applied the new criteria to a large cohort of vertigo patients. Our findings demonstrate that a large proportion of patients with migraine features suspected of VM do not meet criteria. Instead, many satisfy criteria for migraine with or without aura despite experiencing significant vertigo. In comparing VM and migraine groups, it was determined that significant symptomatic overlap exits. These patients reported similar migraine, vertigo and quality of life characteristics. As such, it is clear that on a symptomatic level the VM and migraine group are equivalent and may belong to the same disease process warranting identical treatment protocols. Furthermore, those not meeting any diagnostic criteria for VM or migraine show a significant difference across all measures. Yet because of this groups relationship to migraine, literature indicates this cohort belongs to a BRV entity.

In all cases, we have demonstrated a clear relationship of migraine and vertigo for all. This association may suggest these patients are experiencing vertigo as a migraine manifestation. Thus, treatment with migraine prophylaxis may help alleviate vertigo symptoms in these patients requiring further therapeutic investigation.

Tables

Table 1: ICHD diagnostic criteria for migraine with and without aura, definitive vestibular migraine and probable vestibular migraine. ⁴⁰

Migraine without aura

- A. At least five attacks fulfilling criteria B-D
- B. Headache attack lasting 4-72 hours
- C. Headache has at least two of the following four characteristics
 - a. unilateral location
 - b. pulsating quality
 - c. moderate or severe pain intensity
 - d. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
- D. During headache, at least one of the following:
 - a. nausea and/or vomiting
 - b. photophobia and phonophobia
- E. Not better accounted for by another ICHD-3 diagnosis.

Migraine with aura

- A. At least two attacks fulfilling criteria B and C
- B. One or more of the following fully reversible aura symptoms:
 - 1. visual
 - 2. sensory
 - 3. speech and/or language
 - 4. motor
 - 5. brainstem
 - 6. retinal
- C. At least two of the following four characteristics:
 - 1. At least one aura symptom spreads gradually over 5 minutes, and/or two or more symptoms occur in succession
 - 2. each individual aura symptom lasts 5-60 minutes
 - 3. at least one aura symptom is unilateral
 - 4. the aura is accompanied, or followed within 60 minutes, by headache
- D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been

excluded.

Definitive	Vestibular	Migraine
Deminitive	vestibului	wingrunne

- A. At least five episodes fulfilling criteria C and D
- B. A current or past history of 1.1 Migraine without aura or 1.2 Migraine with aura
 - a. Based on dx above
- C. Vestibular symptoms of moderate or severe intensity, lasting between 5 minutes and 72 hours.

D. At least 50% of episodes are associated with at least one of the following three migrainous features:

- a. headache with at least two of the following four characteristics:
 - i. a) unilateral location
 - ii. b) pulsating quality
 - iii. c) moderate or severe intensity
 - iv. d) aggravation by routine physical activity
- b. photophobia and phonophobia
- c. visual aura
- E. E. Not better accounted for by another ICHD-3 diagnosis or by another vestibular disorder

Probable Vestibular Migraine

A. At least 5 episodes with vestibular symptoms of moderate or severe intensity, lasting 5 min to 72 hours

B. Only one of the criteria B and C for vestibular migraine is fulfilled (migraine history or migraine featu during the episode)

C. Not better accounted for by another vestibular or ICHD diagnosis8Vestibular symptoms of moderate minutes and 72 hours.

Table 2: Demographic composition of population cohort according to diagnosis.

	VM (n=104)	Meet no criteria (n= 192)	P-value	VM (n=104)	Migraine only (n=100)	P-value
Sex (female)	71 (68%)	122 (64%)	0.247	71 (68%)	70 (70%)	0.88
Age (SD)	49 (16)	56 (16)	0.001	49 (16)	53 (14)	0.054

* Table entries are mean (SD) unless otherwise noted; p-values computed using independent samples t-test for continuous variables and Fisher's exact test for dichotomous variables

	VM (n=104)	Meet no criteria (n= 192)	P-value	VM (n=104)	Migraine only (n=100)	P-value
First vertigo episode in years back (SD)	7 (9)	7 (10)	0.873	7 (9)	6 (10)	0.608
Age of first vertigo episode	41 (16)	49 (17)	0.001	41 (16)	48 (16)	0.01
Number of vertigo episodes per day (SD)	1.7 (4)	1.7 (3)	0.9	1.7 (4)	3 (5)	0.191
Duration of vertigo in hours (SD)	11 (22)	23 (78)	0.128	11 (22)	84 (146)	<0.001
Vertigo accompanied by migraine headache	89 (87%)	54 (31%)	<0.001	89 (87%)	61 (63%)	<0.001
Vertigo symptoms and triggers						
Positional vertigo	91 (88%)	150 (78%)	0.06	91 (88%)	83 (83%)	0.431
Rotational vertigo	80 (77%)	109 (57%)	0.001	80 (77%)	65 (65%)	0.066
Vertigo triggered by visual motion	81 (78%)	110 (57%)	<0.001	81 (78%)	72 (72%)	0.338
Cochlear symptoms with vertigo						
Ear pressure	68 (65%)	98 (52%)	0.036	68 (65%)	54 (57%)	0.306
Tinnitus	71 (68%)	97 (51%)	0.003	71 (68%)	59 (59%)	0.191
Hearing Loss	44 (44%)	76 (43%)	0.9	44 (44%)	37 (42%)	0.769

Table 3: Vertigo history, triggers and symptoms of population cohort according to diagnosis.

* Table entries are mean (SD) unless otherwise noted; p-values computed using independent samples t-test for continuous variables and Fisher's exact test for dichotomous variables

		Meet no criteria			Migraine only	
	VM (n=104)	(n= 192)	P-value	VM (n=104)	(n=100)	P-value
First migraine episode in years back (SD)	13 (14)	14 (16)	0.729	13 (14)	16 (16)	0.147
Age of first migraine	36 (16)	37 (19)	0.702	36 (16)	36 (18)	0.973
How often migraine episodes occur per week (SD)	4 (9)	4 (9)	0.839	4 (9)	3 (6)	0.501
Duration of migraine headache in hours (SD)	11 (22)	24 (78)	0.128	11 (22)	84 (146)	<0.001
Family history of migraine	27 (26%)	34 (18%)	0.1	27 (26%)	35 (35%)	0.173
Report personal history of migraine	104 (100%)	127 (66%)	<0.001	104 (100%)	91 (91%)	0.001
History of sinus headache	57 (57%)	81 (46%)	0.103	57 (57%)	66 (69%)	0.105
Unilateral symptoms associated with	(()	/ />		(()	()	
migraine	80 (82%)	82 (86%)	0.435	80 (82%)	69 (80%)	0.852
Allodynia	20 (20%)	9 (6%)	0.001	20 (20%)	28 (32%)	0.094
Commente and side of which asigns in a						
Symptoms associated with migraine		6 6 (4 = 6 ()				
Pulsation or throbbing pain	61 (59%)	26 (15%)	<0.001	61 (59%)	59 (62%)	0.773
Visual symptoms	42 (41%)	0 (0%)	<0.001	42 (41%)	39 (41%)	1
Weakness	48 (46%)	1 (0.6%)	<0.001	48 (46%)	51 (53%)	0.396
Difficulty speaking	28 (27%)	0 (0%)	<0.001	28 (27%)	23 (24%)	0.746
Nausea	61 (59%)	16 (9%)	<0.001	61 (59%)	50 (52%)	0.394
Sensitivity to light	77 (74%)	19 (11%)	<0.001	77 (74%)	65 (68%)	0.352
Sensitivity to sound	75 (72%)	20 (12%)	<0.001	75 (72%)	63 (66%)	0.36
Drowsiness	53 (51%)	8 (5%)	<0.001	53 (51%)	45 (47%)	0.575
Lightheadedness	69 (66%)	24 (14%)	<0.001	69 (66%)	54 (56%)	0.149
Migraine triggers						
Menstruation	48 (68%)	42 (41%)	0.001	48 (68%)	39 (71%)	0.703
Certain foods	20 (21%)	6 (5%)	<0.001	20 (21%)	27 (33%)	0.091
Sleep disturbances	64 (65%)	37 (28%)	<0.001	64 (65%)	51 (59%)	0.543
Physical activity	38 (37%)	12 (6%)	<0.001	38 (37%)	33 (33%)	0.66
Bowel movements	16 (18%)	5 (5%)	0.002	16 (18%)	14 (19%)	1

Table 4: Migraine history, triggers and symptoms of population cohort according to diagnosis.

* Table entries are mean (SD) unless otherwise noted; p-values computed using independent samples t-test for continuous variables and Fisher's exact test for dichotomous variables

	VM (n=104)	Meet no criteria (n= 192)	P-value	VM (n=104)	Migraine without VM (n=100)	P-value	
Global QOL	2.4 (1)	3 (1.4)	0.008	2.4 (1)	2.9 (1)	0.031	
Mental domain	3 (1)	3.5 (.9)	0.005	2.9 (1)	3.1 (.9)	0.353	
Physical domain	2.9 (.8)	3 (.6)	0.225	2.9 (1)	2.9 (.7)	0.695	
Social domain	3 (1)	3.5 (1)	0.006	2.9 (.9)	2.9 (.6)	0.025	
Perceived stress score (SD)	19 (8)	15 (8)	0.004	19 (8)	16 (8)	0.148	

Table 5: Quality of life and perceived stress score compared across the three diagnostic groups.

* Table entries are mean (SD) unless otherwise noted; p-values computed using independent samples t-test for continuous variables and Fisher's exact test for dichotomous variables

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