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VESTIBULAR MIGRAINE-UPDATES AND CHALLENGES: REVIEW OF LITERATURE

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ABSTRACT Complaints of dizziness or vertigo entirely are common in patients with migraines, at least occasionally. Vestibular migraine was recently integrated as an independent article in the International Classification of Headache Disorders 3-beta appendix. Despite this, it is still an underdiagnosed condition. The exact mechanism of vestibular migraine is still unclear. This review presents an overview of the history, epidemiology, pathophysiology, clinical characteristics, diagnostic criteria, differential diagnosis and the treatment of VM.

KEYWORDS : Vestibular migraine, Headache, Dizziness, Vertigo, Migraine

INTRODUCTION

Complaints of dizziness or vertigo are common in patients with migraines and can be reported by up to 30–50% of subjects, at least occasionally.[1] Recently, there was an increased interest in these issues due to the finding, in epidemiological studies, that the co-occurrence of those two conditions was higher than expected from the combined prevalence of both disorders in the general population and the estimation that vestibular symptoms associated with migraine can represent the most common form of vertigo.[2] Vestibular migraine (VM) was recently integrated as an independent article in the International Classification of Headache Disorders 3-beta (ICHD-3 beta, A1.6.5) appendix.[3] This designation and diagnostic criteria were from a consensus document published by the Bárány Society (International Society for Neuro-otology) and the International Headache Society (IHS), established by a collaboration between neurologists and otorhinolary ngologists. Nevertheless, the broad definition for this disorder has been criticized due to a lack of specificity.[4,5] Vertigo of vestibular origin affects about 7.4% of the general population, and migraine is more common, affecting 12–16% of the population.[1,2,6]

A plethora of terms has been used to label the relationship between migraine and vertigo, including migraine-associated dizziness, migraine-associated vertigo, migraine-related vestibulopathy, benign recurrent vertigo migrainous vertigo. In recent times, the term VM was defended as an entity covering the vestibular manifestations of migraine, avoiding confusion with non-vestibular dizziness that may be associated with migraine.[7]

HISTORY

Despite the well-known relationship between vertigo and migraine in children, the association between migraine and vestibular symptoms in adults was first recognized in 1984.[8,9,10] Bickerstaff, in 1961 made the first description of migraine with brainstem symptoms, including vertigo, and named it basilar artery migraine in patients with the same symptoms, suggesting an abnormality in basilar artery circulation. He referred to the earliest recorded description of basilar artery migraine by Aretaeus of Cappadocia in 131 BC.[11] In 2004, the International Headache Society (IHS) had reclassified it as basilar migraine, considering the ambiguity of basilar artery involvement.[12] Recently, in the ICHD-3 beta classification, it became known as migraine with brainstem aura (MBA).[3]

In 1999, Boenheim used the term VM for the first time. Neuhauser et al., in 2001, proposed the diagnostic criteria for Migrainous Vertigo, widely used since then.[13,14] In 2013, a working group (Bárány Society and IHS) established an expert consensus on the diagnostic criteria currently in use, included in an appendix of the third edition of the International Classification of Headache Disorders.**3** However, the clinical features of this entity are still under discussion and are still a matter of research.

EPIDEMIOLOGY

Even though VM is the second most common cause for dizziness (after benign paroxysmal positional vertigo), accounting for nearly 6-9% of all diagnoses, it is still underdiagnosed.[13,15] In the study conducted by a specialized Swiss clinic, dizziness was diagnosed as vestibular migraine in 20.2% of patients, although the referring physicians previously suspected VM in only 1.8% of patients. The diagnosis of "uncertain dizziness" accounted for roughly 60% of patients.[7] In another German study with 33 patients, 66% of patients diagnosed with VM had consulted a doctor due to vertigo, but only 20% were diagnosed with VM. The remaining patients were diagnosed with other conditions such as anaemia, hypovolemia, diabetes.[16] VM has a year prevalence of 0.89% and represents about 10% of patients treated for either migraine and dizziness.[17] Hsu and colleagues observed a year prevalence of vestibular migraine in women aged 40-54 years of 5%.[18] 40% of patients with VM reported missing work because of their symptoms, showing the impact of the disease on daily life.[16] VM can occur at any age, but the average age of onset for dizziness in migraine is about 40. It has a female predominance, a female and male ratio of 5:1.[16,19] In elderly patients, particularly post-menopausal women, typical migraine attacks can sometimes be replaced by isolated episodes of vertigo, dizziness or a fleeting feeling of imbalance.[20] In a population-based study, the pervasiveness of recurrent vertigo related to migraine was estimated at around 2.8% in children with 6-12 years.[21] VM is diagnosed more often in children than adults (35% vs 6%).[22] The most typical cause of vertigo in children is benign paroxysmal vertigo, strongly associated with a familial history of migraine and may predict the development of typical migraine.[23]

PATHOPHYSIOLOGY

The exact pathophysiology of VM is unclear, and a majority of the theories published so far focus on the complex neural interactions of migraine without clearly explaining vertigo. However, the interaction between the vestibular and nociceptive systems seems to be quite intuitive due to an evident and tight association between the vestibular structures and brainstem areas related to the processing of pain such as the locus coeruleus, dorsal raphe nuclei, the lateral tegmentum, and connections between lateral, inferior and caudal vestibular nucleus and the caudal trigeminal

nucleus.[22] These nuclei's thalamus afferent pathways are near and connected with common areas related to pain and vestibular cortex, insular cortex, orbitofrontal cortex, and the cingulate gyrus and strongly suggests the interaction and connection between the two.[24]

The evidence supporting the notion that the anatomical proximity of these structures justifies their intervention in the pathophysiology of VM is scarce. However, a few experiments described a strong connection and increased signal transmission between the nociceptive system and the vestibular nuclei when comparing VM patients with controls. Some experimental animal models also stressed this relationship and the activation of a trigeminovascular reflex within the inner ear as a possible mechanism for local dysfunction in VM. In guinea pigs, ophthalmic branch of the trigeminal nerve directly innervates the cochlear blood vessels, and the stimulation of this nerve led to vasodilation within the inner ear with increased vascular permeability and extravasation of plasma, proteins, and serotonin.[25] In humans, by using painful electrical stimulation on the skin area innervated by the trigeminal nerve (at the supraorbital point), in patients diagnosed with VM, nystagmus could be induced or modified (increased). At the same time, in healthy controls, nothing could be observed in the same experimental conditions.[25,26,27] These observations were interpreted as a sign of direct vestibular stimulation by the trigeminovascular system.

Vestibular manifestations are associated with cortical hyperexcitability and central sensitization of the trigeminal system, in migraine patients, due to a specific impact on the vestibular system.[25] Several studies later corroborated the hyperexcitability of the vestibular system in migraine patients.[28,29] Hyperexcitability of vestibulothalamocortical pathways is associated with cerebellum activation and hypoactivity of occipital lobes, eventually suggestive of reciprocal inhibition between visual and vestibular systems.[24] Murdin et al. observed a decreased suppression of otoacoustic emissions when comparing VM patients with controls.[29] Lewis et al. showed that the perceptual threshold for dynamic head movements was reduced in vestibular migraine patients compared with healthy controls.[28] The cause of this vestibular system impairment, inferred to result from cortical hyperexcitability, is not clear. Nevertheless, the premise of a "locus minoris resistentiae," though unverified, seems to be plausible; the susceptibility results from conditions affecting the vestibular system (such as neuritis) based on a preexisting migraine.

The theory of "cortical spreading depression" has been invoked to explain the vertigo mechanism in VM.[30] Nevertheless, it is unlikely to have a cortical spreading depression on the brainstem (and cortex) without causing other relevant signs or symptoms. Extracellular and neocortical release of molecular signals during cortical spreading depression may lead to the activation of the trigeminal afferents on cranial blood vessels, and this critical step would elicit trigeminovascular reflex-mediated vasodilatation in the meninges. This response would initiate a sterile inflammatory response extending up to the inner ear, as demonstrated by the animal models.[26,27] These local vascular changes may lead to balance abnormalities, which plays a role in VM pathophysiology.

Notwithstanding, vasodilatation is neither necessary nor sufficient for the perception of pain, and this is where the trigeminal afferent activation in the ascending thalamocortical pathways comes into the picture.[31] These pathways comprise regions and structures currently established as a central migraine circuit, including central vestibular pathways. Data from human functional imaging studies show that regions typically involved in the perception of migraine pain (such as the anterior and posterior insula, cingulate gyri, and the orbitofrontal cortex) are activated.[24,32] Additionally, the caudal parabrachial nucleus also receives trigeminal nociceptive and vestibular inputs, contributing to motion hypersensitivity in migraine patients.[33] The parabrachial nucleus is in a close association with the amygdala, in which there is a grand expression of stress-response receptors. This suggests the role of stress in the development of migraine signs and symptoms and also points to the existence of a cognitive-behavioural aspect in the disease and an interoceptive performance that seems to be inflected by the dorsal raphe nucleus and the locus coeruleus.[22,34]

The association between migraine and episodic ataxia type 2, which is associated with disturbances in balance, raised the hypothesis of VM to be a channelopathy.[35] Mutations in the CACNA1A gene (which encodes a voltage-dependent calcium channel) were described both in familial hemiplegic migraine and in episodic ataxia type 2, making plausible a genetic link between vestibular disorders and migraine.[36] However, it was impossible to determine a consistent genetic defect involving the CACNA1A gene in VM patients.[35] The gene encodes for a calcium channel principally expressed in the cerebellum and may explain why patients of familial hemiplegic migraine with CACNA1A mutations may regularly report central vestibular signs and symptoms. Even in migraine with aura patients, not tormented by familial hemiplegic migraine and not having any CACNA1A mutations, a dysfunction of calcium channels has been described, suggesting a more generalized problem among patients with migraine.[37]

Given such intricacies, not only in anatomical grounds but also in terms of neurochemical organization of vestibular and pain pathways, it is evident that more studies are necessary to understand VM pathophysiology and the features underlying the success of a pharmacological treatment, where this component is critical for the design of successful clinical trials for VM.

DIAGNOSTIC CRITERIA

The Bárány-Society (International Society for Neuro-Otology) and the International Headache Society (IHS) created a consensus diagnostic criteria for VM, added in the appendix of the new ICHD-3 beta version of the International Headache Classification.[3]

(A) ≥5 episodes with vestibular symptoms of moderate or severe intensity, lasting 5 min to 72 h.

(B) Previous or current history of migraine with or without aura according to the International Classification of Headache Disorders.

(C) One or more migraine components with at least 50% of the vestibular episodes:

- headache with ≥2 of the following characteristics: unilateral, pulsating quality, moderate or severe pain intensity, aggravated by physical activity
- visual aura,
- photophobia and phonophobia.

(D) Not better accounted for by any other vestibular or ICHD diagnosis.

Probable vestibular migraine

(A) ≥5 episodes with vestibular symptoms of moderate or severe intensity, lasting 5 min to 72 h.

(B) Only one of the criteria B and C for VM is fulfilled (migraine history or migrainous features during the episode).

(C) Not better accounted for by any other vestibular or ICHD diagnosis.

CLINICAL FEATURES

VM often begins several years after a typical migraine.[13,19] In a previous study, migraine has manifested before VM in 74% of participants, and in 52%, migraine preceded VM by more than five years, and in 26% even by more than ten years. The 85% of patients had experienced both VM and migraine during the last 12 months.[16] VM is more common in patients without aura than in patients with aura.[22] The most frequent vestibular symptoms associated with migraines are spontaneous vertigo in 67%, followed by positional vertigo in 24% of the patients.[16] Other commonly described features are imbalance, head motion intolerance, visual vertigo and non-vertiginous dizziness such as lightheadedness or "boat-like" rocking.[17,38]

The duration of attacks may vary from a few seconds (10%) to some minutes (30%), some hours (30%) and even up to a few days (30%).[4] Only 10-30% of patients experienced a typical vestibular aura. Vestibular symptoms can occur during, before or after migraine attacks, and in 30% of the patients, the two symptoms never occurred together.[13,39] Some patients described vertigo as the most disabling symptom.[30,40]

Auditory symptoms, including tinnitus, hearing loss, and aural pressure, have been reported in up to 38% of patients with VM. Hearing loss is usually transient and mild, without or with only minor progression in the course of the disease.[13]

The same triggers can bring about episodes of VM as those for migraine headache, including irregular sleep, stress, physical exertion, menstruation, dehydration, food and drinks, and intense sensory stimulation, primarily movement.[22]

In most patients, the otologic and neurologic examination is regular during the interictal phase.[30] About 10 to 30% of patients with VM have unilateral hypoexcitability to caloric stimulation, and 10% have a directional preponderance for nystagmus responses. Such findings, however, are not specific to VM.[41] In one study, patients with VM became nauseous after caloric testing four times more often than migraine patients and patients with other vestibular disorders.[42] A neuro-otologic study of 20 patients in the acute phase of VM showed pathological nystagmus in 14 patients, primarily central spontaneous or positional nystagmus. Three patients had peripheral spontaneous nystagmus and a unilateral deficit of the horizontal vestibulo-ocular reflex. An imbalance was observed in all patients except one.[43] Since there are no specific abnormalities in VM, the diagnosis will be based on the patient's clinical history in general practice.

DIFFERENTIAL DIAGNOSIS

BPPV is the most frequent cause of recurrent vertigo.[44] BPPV leads to episodes of short-lasting vertigo typically lasting weeks to months without therapy. During acute vertigo attacks, the positional nystagmus analysis usually permits differentiation of positional VM from BPPV.[45]

The primary differential diagnosis of VM is Ménière's disease (MD). MD is a chronic progressive disease characterized by two or more recurrent episodes of spontaneous vertigo, lasting 20 minutes to 12 hours and a fleeting low to medium frequency sensorineural hearing loss in the affected ear during, before, or after one of the vertigo episodes on at least one instance, as well as ipsilateral fluctuating aural symptoms (ear fullness or tinnitus). Other causes must be excluded. The significant difference distinguishing definite from probable MD is the audiometric documentation of the hearing loss.[46] Some studies have ratified a higher prevalence of migraine in patients with MD. Almost 30% of patients with MD may also have VM.[47] The coexistence of both diseases may make the patient's diagnosis difficult, and the most reliable distinguishing feature is the low-frequency hearing loss in MD.[48] It is not easy to differentiate between these entities. Ménière first described this relationship in 1861 and labelled it apoplectiform cerebral congestion.[49]

In most cases, the evolution of disease with time allows the differential diagnosis. Initially, the symptoms can be identical, but MD's progressive loss of hearing happens with or without vertigo. MD also predisposes to BPPV, eventually.[50,51,52] Also, migraine is three times more common in patients with idiopathic BPPV than in BPPV secondary to trauma.[51] The correct diagnosis is essential for treatment and prognosis.

Transient ischemia in the vertebrobasilar system is a prevalent cause of episodic vertigo in the elderly. It is abrupt in onset, typically lasts several minutes, and is frequently associated with nausea and vomiting. Baloh studied 42 patients with vertebrobasilar insufficiency and found that 62% of them had at least one isolated episode of vertigo, and in 19%, the transient ischemic attack began with an isolated episode of vertigo.[53] Therefore, it is reasonable to investigate elderly patients with sudden onset of unilateral deafness and vertigo, mainly if a prior history of TIA, stroke or known atherosclerotic vascular disease is present.

Basilar migraine requires the presence of at least two aura symptoms, which are attributed to the vertebrobasilar territory, lasting between 5 to 60 minutes and followed by a typical migraine headache.[4] Fewer than 10% of the patients with VM meet the required criteria for basilar migraine.[13]

Somatoform vertigo is also common in adults and children.[54,55] Anxiety is a common comorbidity of migraine and is frequently associated with vestibular disorders, especially with VM. A new disorder named migraine–anxiety-related dizziness (MARD) has been proposed.[56] MARD is a condition that must be considered as recurrent dizziness can cause debilitating anxiety. This disease is diagnosed with symptoms of anxiety, migraine, and vestibular symptoms. Treating anxiety as well as migraine and balance disorder is a must.

Vestibular paroxysmia (probably caused by vascular compression of the vestibular nerve) syncope, and orthostatic hypotension are other possible differential diagnosis.[4]

TREATMENT

Only a few randomized controlled clinical trials have been conducted on the specific treatment for VM: during the attack or as prophylaxis. Two of the studies used triptans for attack therapy.[57,58] One study reported that 38% of patients with VM attacks benefitted from 5 mg zolmitriptan, whereas only 22 % in the placebo group showed a beneficial effect. However, the validity of this study is limited due to its small number of patients (n = 10) who reported only 17 attacks and large confidence intervals.[57] The other randomized, double-blind, placebo-controlled study with rizatriptan vs placebo measured how motion sickness responded to a complex vestibular stimulus. 25 migraineurs with or without migraine-related dizziness participated. 13 of the 15 participants who reported vestibular-induced motion sickness showed a decline in motion sickness after taking rizatriptan compared to the placebo ($p<0.02$). However, this benefit was not noticed after exposure to more intense vestibular stimuli. It was suggested that rizatriptan decreased vestibular-induced motion sickness by influencing serotonergic vestibular-autonomic projections.[58]

Prophylactic treatment was recently analyzed in The Cochrane Collaboration for randomized controlled trials in adults with VM diagnosis or probable VM according to the Bárány Society/IHS criteria.[59] Only 1 out of 558 studies could be identified based on the new criteria for VM and met the necessary study conditions. This study comparing metoprolol vs placebo is still ongoing.[60] Most therapeutic recommendations for VM prophylaxis are based on the

therapy guidelines for migraine with and without aura. Therapeutic approaches to VM are found in case reports, retrospective cohort studies, and open-label trials.

A large retrospective evaluation of 100 patients compared VM patients with and without prophylactic migraine treatment.[61] All patients on prophylactic treatment showed decreased duration, intensity, and frequency of episodic vertigo and its associated features ($p < 0.01$). The drugs taken were metoprolol (median dose 150 mg), propranolol (median dose 160 mg), valproic acid (median dose 600 mg), topiramate (median dose 50 mg), butterbur extract (median dose 50 mg), lamotrigine (median dose 75 mg), amitriptyline (mean dose 87.5 mg), flunarizine (5 mg), or magnesium (median dose 400 mg). The group not receiving prophylactic therapy and following a modified lifestyle only showed a reduction of vertigo intensity.[61]

Another retrospective study of 100 patients with migraine-associated dizziness also reported benefits from migraine prophylaxis.[62] A third retrospective cohort of 33 patients with recurrent migraine and vertigo attacks: the attack frequency was wholly reduced in 57.6 %, reduced by over 50 % in 24.2 %, and reduced by less than 50 % in 15.2 %; there was no decrease in one patient. In this study, 12 received took propranolol, 11 took clonazepam, seven flunarizine, two metoprolol, and another two patients received amitriptyline.[63]

Smaller studies have reported on the effects of single drugs for migraine prophylaxis. Sodium valproate did not reduce the vestibular symptoms in 12 VM patients but had a considerable effect on migraine headache in eight.[64] Cinnarizine was tested in a single-centre, open-label retrospective investigation on VM and migraine associated with vertigo.**65** The study included 24 patients with VM and 16 with basilar-type migraines. The ages ranged from 18 to 54 years (mean 30 years). The mean frequency of vertigo and the mean frequency, duration, and intensity of migraine headaches per month were significantly reduced after three months of cinnarizine therapy (all $p<0.001$).[65] This exciting data will have to be reconfirmed in a large-scale, randomized, controlled clinical trial.

Flunarizine was tested to treat migraines without aura and the treatment of vertigo in two extensive open-label post-marketing studies.[66,67] In both studies, flunarizine showed considerable efficacy compared to propranolol (for migraine) or betahistine (for vertigo). However, both studies did not include VM patients specifically, and thus, the efficacy of flunarizine for this condition remains unproven. The only randomized controlled study of one tertiary academic centre compared the effects of flunarizine in 48 patients with VM over 12 weeks with those getting 16 mg betahistine and vestibular exercises.[68] Flunarizine treatment reduced the frequency of vertiginous episodes ($p = 0.010$), and the severity of vertigo improved ($p = 0.046$). However, the frequency and severity of headaches were not significantly different in the two groups. Side effects of flunarizine were somnolence and weight gain.[68]

A retrospective study evaluated the effects of flunarizine and propranolol in 61 VM patients. Flunarizine patients ($n = 30$) showed a 68 % response rate to symptoms of VM ($p<0.001$), while patients receiving propranolol ($n = 31$) had a73% response rate ($p<0.001$).[69]

A trial reported successfully treating migraine auras, isolated auras, and migraine-associated headaches to a lesser extent with lamotrigine.[70] Another open-label, retrospective study demonstrated moderate efficacy of 100 mg lamotrigine in 19 VM patients over 3–4 months. Headache frequency fell from 8.7 to 4.4 (average per month), vertigo frequency decreased from 18.1 to 5.4 (average per month), but this was not statistically significant. Therefore, lamotrigine may reduce vestibular symptoms primarily, but headache only to a less extent.[71]

One study investigated the combination of caffeine abstinence and treatment with nortriptyline and topiramate in 34 patients with VM. Improved symptoms were reported by 14% of the patients who abstained from caffeine. In comparison, nortriptyline reduced dizziness in 46%, and topiramate reduced symptoms in 25 % of patients ($p = 0.007$). Thus, 75 % of VM patients had a meaningful benefit from these therapeutic interventions; consequently, they did not switch to othertreatments.[72]

Less common migraine treatment medications include benzodiazepines, selective serotonin reuptake inhibitors (SSRI), dothiepin, pizotifen, acetazolamide, and behavioural modification, including special diets reported positive effects in VM.[63] However, therapeutic recommendations for the specific treatment of VM cannot be made hastily. Moreover, there were inconsistencies in defining VM in many of the studies, especially the older ones, so that the studied cohorts were quite heterogeneous. The latest diagnostic criteria will eradicate this confusion in future studies, leading to more comparable, better quality results.

Vestibular rehabilitation proved effective in VM as an add-on treatment to medical therapy or a stand-alone therapy. 20 VM patients and 16 patients with vestibular impairment suffering from daily vestibular symptoms participated in a 9-week vestibular rehabilitation program. While the VM group demonstrated lower subjective performance at the onset of therapy, both groups benefitted equally from rehabilitation.[73]

CONCLUSION

The future perspectives for both clinical and basic science studies exploring the pathophysiology of VM are promising. Recognizing the neurochemical organization of the vestibular, nociceptive, and cognitive pathways and their interactions will provide realistic strategies for treating the disorder. More research is needed to clarify the possibility of genetic mechanisms leading to a greater susceptibility for VM. Multicenter randomized controlled trials based on pathophysiology must now be designed based on the recently established diagnostic criteria for the effective treatment of VM.

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