

VESTIBULAR MIGRAINE: CHALLENGE AND RECENT KNOWLEDGE

I Made Oka Adnyana*, Putu Lohita Rahmawati** and I Putu Eka Widyadharma*¹

*Staff at Departement of Neurology University of Udayana Sanglah Hospital, Denpasar, Indonesia., **Neurology Resident, Faculty of Medicine, Udayana University Sanglah Hospital, Bali, Indoensia.

ABSTRACT Vestibular migraine (VM) is a clinical problem presented as a combination of headache with vertigo, dizziness, and balance disorder. It is the primary cause of recurrent vertigo with a long life prevalence of up to 1%. Recently, there is growing evidence of connection or interaction between the nociceptive system with the vestibular tract in the human brain. However, the exact pathomechanism of VM has yet to be identified. VM is included in the appendix of The International Classification of Headache-3 (ICH-3). However, this clinical entity, which has been introduced since the 19th century, is still one of the significant challenges for clinicians worldwide. There are no diagnostic tools for VM, make it a is pure clinical diagnosis demanding clinician's skill to be identified. This review article aims to compile from numerous literature regarding recent knowledge related to VM, including its definition, epidemiology, pathophysiology, clinical presentation, diagnosis, differential diagnosis, and treatment modality.

KEYWORDS vestibular, migraine, vertigo

Introduction

The connection between migraine and vertigo has been introduced since Lieving, in 1873, published his review about headache and related symptoms. However, systematic studies about migraine-related vertigo started a century later. The terminology of VM as a diagnosis entity has just introduced for the last thirty years. This terminology has been widely used in clinical and study purposes since then event hough there were no established diagnostic criteria.[1] The interaction between the nociceptive system and the vestibular tract was proposed as the underlying pathophysiology of VM. Also, some studies reported that people who are genetically prone to migraine are also susceptible to vertigo related to head movement.[2]

The diagnosis criteria for VM was made in 2012 by Barany Society and the International Headache Society (IHS).[1] However, VM is still a big challenge for clinicians. The diagnosis was made

solely based on clinical examination by the physicians. There are no specific diagnostic tools to confirm the clinical findings. Due to those complications and uncertainty, clinicians should rule out other causes of vertigo and migraine before diagnosing a patient with VM.[2]

This review is aimed to explore the recent knowledge about VM, including its epidemiology, pathophysiology, clinical features, and diagnostic procedure. It is also reviewing all therapy modalities available for migraine and vertigo, which may be a benefit to VM patients in controlling the disease.

Discussion

A. Definition and historical aspect

There has been a long history of clinicians, mainly neurologists, reporting patients suffering both migraine and vertigo. Initially, various terms were used to identify the condition, including migraine-associated vertigo, migraine-associated dizziness, migrainous vertigo, and migraine-related vestibulopathy.[3] Those terms show that in the past, vertigo in migraine patients was considered as one of the symptoms of migraine. Thus, before the International Classification of Headache Disorders 3rd Edition (ICHD-3), the IHS described it as one of aura in basilar migraine.[4]

VM as a separate diagnostic entity was recommended for the

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Associate Editor: Ivan Inkov (BG);

¹Staff at Departement of Neurology University of Udayana Sanglah Hospital, Denpasar, Indonesia; Email:eka.widyadharma@unud.ac.id

first time by Neuhauser.[3] The diagnostic criteria were revised by Barany Society in collaboration with IHS in 2012. Recently, the IHS included VM in the appendix of ICHD-3 with a diagnostic code of A1.6.6 under the group of episodic syndromes that may be associated with migraines. Diagnostic criteria that are included in the appendix of ICHD-3 are new diagnostic entities that are factually found in clinical practice but have not supported by enough evidence to be formally included in the ICHD. Further researches are still needed to establish valid diagnostic criteria.[5] The same VM criteria are also included in the Classification of Vestibular Disorders of the Barany Society (Tabel 1). In addition to the VM criteria, Barany Society is also introducing criteria of probable VM (Tabel 2).

B. Epidemiology

VM is one of the most common causes of recurrent spontaneous vertigo with a reported lifetime prevalence of 1% and a year prevalence of 0,9% in the general population.[6] The prevalence is higher among patients visiting dizziness clinics, with an estimation of 7%.3. The prevalence is even higher among migraine patients, which are estimated to reach 10,3%.5] MV is 1,5 to 5 times more frequent in females than males.[3] Hormonal is suspected as the factor underlying this feature in addition to other precipitating factors such as stress, sleep disturbance, certain foods, and dehydration. Most of the patients with VM have been already suffering from migraines for a long period, with an average of 8,4 years.[7] In a post-menopause woman with a history of migraine, the unilateral headache was reported to be replaced with an episode of vertigo.[8]

VM, as identified in migraine, has a genetic basis of autosomal dominant inheritance pattern with lower penetration in male.[7] Gen for VM has been identified in chromosome 5q35 in locus between rs244895 and D5S2073 with an interval of 12,0MB.[9]

C. Pathophysiology

The exact pathomechanism of VM is yet to be explained. However, there is a growing hypothesis that VM is caused by parallel activation of the nociceptive pathway and vestibular tract. Genetic susceptibility in VM patients leads to an increase in neuronal excitability during the processing of sensory information. The increasing excitability induces interaction between the pain tract and vestibular tract in a different part of the brain, including the inner ear, brain stem, thalamus, and cortex.[7]

Vascular regulation of the peripheral vestibular system

Inner ear structures, which consist of cochlea and vestibulum, get vascular supply from the inferior anterior cerebellar artery, which is one of the basillary artery branches. The axons from trigeminal neurons are responsible for maintaining the vascular tone of the extra parenchymal intracranial artery. Thus, vascular regulation of the peripheral vestibular system is similar to those in the brain. The fibres from trigeminal neurons release a neurotransmitter that is causing dilatation of intracranial arteries which in turn generate headache.[7]

Vass et al. in 1998 proved the hypothesis mentioned above. They investigated the role of trigeminal ganglion projection in the inner ear vascular system. They injected biocytin into the trigeminal ganglion of guinea pigs and found a significant amount of labelled fibres in the spiral artery of the inner ear.[10]

Trigeminovascular reflex is responsible for vascular dilatation and plasma extravasation. This process results in meningeal inflammation. A similar mechanism of plasma extravasation is also identified in the inner ear of migraine induced animal models.[7]

Phenotype similarity of neurochemical receptor in the nociceptive and vestibular system

Several experimental studies reported that nociceptive and vestibular systems have similar neurochemistry receptor properties. Vestibular and nociceptive systems meet in several structures in the brainstem including the parabrachial nucleus, raphe nucleus, and locus cereleus (Picture 1) which are important in pain modulation process and affective responses to pain.[7] Within those structures, there is an additive effect in processing information from vestibular and nociceptive afferent.

Vestibular ganglion, spiral ganglion, and trigeminal ganglion have similar serotonin receptors distribution, including 5-HT1B, 5-HT1D, dan 5-HT1F, Purinoseptor (P2X3) dan Capsaicin (TRPV1). In addition to those receptors, trigeminal ganglion also has CGR_p receptors. The latest receptor cannot be found in vestibular ganglion.[11]. Similar receptors expression can also be found in the spiral ganglion and cochlear ganglion. This phenomenon explains auditory symptoms in migraine, such as phonophobia and tinnitus.[11]

Thalamic and cortical projection similarity of vestibular and nociceptive systems

Functional imaging examination shows that cortical areas that are activated by vestibular stimuli are also involved in pain perception. Those areas include anterior and posterior parts of the insula, orbitofrontal cortex, and cingulate gyrus. Increasing metabolic rate on those areas was reported on fMRI examination during VM attack. The opposite effect was reported in the occipital area. This finding was interpreted as a reciprocal inhibition mechanism between visual and vestibular systems.[7]

A study by Russo et al in 2014 reported thalamic's role in VM pathophysiology.[12] Caloric stimulation was done into three groups. Those groups were a group of normal control, a group of patients with migraine without aura and a group of patients with VM. Subsequent fMRI examination done to all subjects found that caloric stimulation activated bilateral insular cortex, right thalamus, right parietal cortex, brainstem (including periaqueductal grey matter) and cerebellar. In the VM group, thalamus activity increased significantly. The underlying mechanism of this phenomenon is yet to be explained until now. However, it is known that the thalamus is a gatekeeper of sensory transmission from the brainstem to the cortex. The cortical perception process depends on the thalamic modulation effect.

D. Clinical features and diagnosis

The diagnosis of VM is purely clinical and depends on anamnesis and neurological examination. Clinicians should perform a thorough examination before conclude that the patient's problem is VM.[7] According to ICHD-3, vestibular symptoms in VM is as defined by Barany Society which include:[5]

1. Spontaneous vertigo that may include internal vertigo (false sensation of self-movement) and external vertigo (a false sensation that the environment spinning around);

Table 1 Diagnostic criteria of VM according to ICHD-3 and the Barany Society.[1,5]

A. At least 5 episodes of vestibular symptoms fulfilling criteria C and D
B. A current or past history of Migraine without aura or migraine with aura
C. Vestibular symptoms of moderate or severe intensity that lasting between 5 minutes to 72 hours
D. At least half of episodes are associated with at least one of the following three migraine features: 1. Headache with at least two of the following four characteristics: a. Unilateral location b. Pulsating quality c. Moderate to severe intensity d. Aggravation by routine physical activity 2. Photophobia and phonophobia 3. Visual aura
E. Not better accounted for by another ICHD-3 diagnosis or by another disorder.

Table 2 Criteria of probable VM according to The Barany Society/ [1]

A. At least five episodes of vestibular symptoms with moderate to severe intensity for 5 minutes to 72 hours
B. Only one from B and C criteria of VM (history of migraine or migraine features during the episode)
C. Not better accounted for by another vestibular or ICHD diagnosis

2. Positional vertigo after changing head position;
3. Vertigo that is induced by a complex and fast-moving visual stimulus;
4. Vertigo that is induced by head movement;
5. Dizziness that is induced by head movement and nausea.

Spontaneous vertigo is reported in 21-83% of VM patients, 17-65% with positional vertigo and intolerance with head movement in 31-7% patients.[7] During VM episode, clinical symptoms that are similar to central vertigo can be identified in physical examination. The symptoms can be in the form of gaze-induced nystagmus, saccadic pursuit, central positional nystagmus, and horizontal or vertical spontaneous vertigo.[7]

Vestibular symptoms mentioned above are categorized as moderate if they do not interfere with the patient's daily activities. Patients with severe symptoms can do nothing but laying down in the bed.[5] Spell duration are various from seconds to days. Approximately 30% of patients have a couple of minutes episodes, 30% of them reported spell that last for hours, 30% patients have long-lasting episode within some days and only 10% reported a very short duration less than a minute. However, vertigo duration included in the present diagnosis criteria of VM is 5 minutes to 72 hours.[5]

Vestibular symptoms in VM can be presented before, during, or after headache. Approximately 25% of patients have a headache first before vertigo, and 30% of patients have vertigo spell without headache. In the last case, patients report another typical migraine symptoms such as photophobia, phonophobia, osmophobia, nausea, and vomitus.[2] Mild and transient hearing loss is reported in 37% of VM patients.[7]

Neurological examination to patients in-between episodes of VM is normal. Some pathology that may produce vestibular

symptoms must be excluded to be accurately diagnosing VM. Vestibular test, audiogram, and neuroimaging usually ordered by clinicians to exclude other conditions with similar clinical appearances. Audiogram and vEMPs are used to differentiate vEMP and Meniere disease. Neuroimaging such as MRI or MR angiography can be ordered if the clinicians suggest that vascular factors contributed to vertigo.[2] Messina in 2016 reported his study that found a substantial change in substantia nigra of the cortex in VM patients. There are increasing in grey substance in the left thalamus, left temporal lobe, frontal lobe, occipital.[13]

E. Differential Diagnosis

1. Meniere disease Meniere disease is the main differential diagnosis of VM. In the early stage of VM, those two conditions are very hard to differentiate because 38% of VM patients have auditory problems and tinnitus. Clinicians must be meticulously detailed in gathering information regarding the auditory symptoms in vertigo patients. Low pitch tinnitus is related to Meniere disease, while most VM patients complaining high pitch tinnitus.7 Auditory problem in Meniere disease is progressive while in VM, it does not always report by patients.[5]

On the other hand, patients diagnosed with Meniere disease reporting unilateral throbbing headache two times more frequently than healthy people. Photophobia is also a common symptom complained by patients with Meniere disease.[5]

There are at least three hypotheses regarding the similarity between Meniere disease and VM. First, Meniere disease and VM are suffered coincidentally by patients. Secondly, endolymphatic hydrops is a consequence of internal ear damage because of VM.[7] Thirdly, Meniere disease and VM are a spectrum of a disease that shares a common genetical

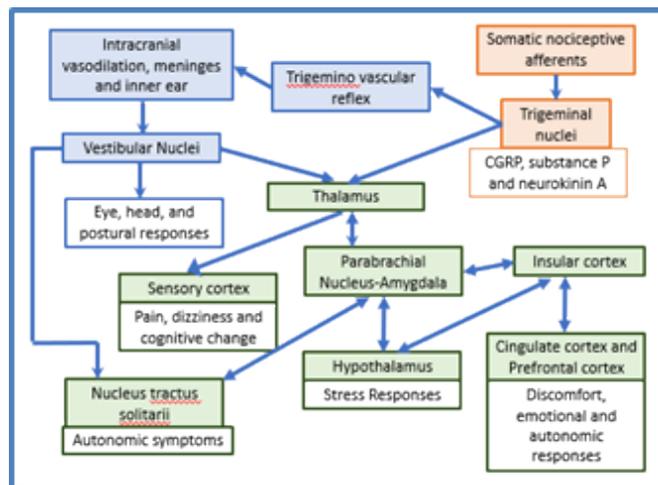
basis.[5] It is too early to consider which one of the hypotheses is accurate. Further research on the pathophysiology of the two diseases is needed. According to ICHD-3, once criteria of Meniere disease is fulfilled, especially when there is objective proof of the auditory problem with audiometry (audiogram or cVEMPs), patients should be treated as having Meniere disease even though the patients reporting migraine-like headache. Double diagnosis of Meniere disease and VM can be made if patients were suffering two separate spells with each spell fulfilling criteria of VM and Meniere Disease.[5]

2. Migraine with aura and migraine with brainstem aura Vestibular symptoms are categorized as aura if the symptoms only happen for 5-60 minutes. As mentioned above, there are only little portions of patients with migraines complaining of a short duration of vestibular symptoms to be regarded as an aura. Diagnosis criteria of migraine with brainstem aura necessitate two brainstem symptoms other than visual and sensory problems or dysphasia. Brainstem symptoms are reported by less than 10% of patients diagnosed as VM.[5]
3. Benign Paroxysmal Vertigo According to ICHD-3, benign paroxysmal vertigo is a disease in children. The disease is considered as an early syndrome of migraine. There should be five episodes of sudden onset vertigo that end spontaneously in minutes to hours. Between the spell, neurologic, audiometry, vestibular function, and EEG are otherwise normal. Throbbing headache can be reported, but it is not mandatory to establish a diagnosis.[5] There is no age limitation in VM criteria, according to ICHD-3. Thus, children with symptoms fulfilling the ICHD-3 criteria for VM can be diagnosed as having VM and treated accordingly.[5]

F. Management

VM is recommended to be treated as a migraine. There is no enough randomized controlled trial in this field until recently. The most cited research reported is one that was performed by Neuhauser et al. regarding Zolmitriptan as abortive therapy. Another therapeutic approach reported in the form of a case report, retrospective cohort, and open-label trials.

1. Abortive Therapy All abortive therapy for migraine is recommended for VM. Sumatriptan, nonsteroidal anti-inflammatory drugs (NSAID) and ergot are reported effective for VM.[13] A study by Neuhauser et al. in 2003 reported 2,5 mg of Zolmitriptan is effective in controlling spell in 38% of VM patients.[15] Zolmitriptan 5 mg is the first choice in an acute spell. Non-oral preparation such as nasal spray, suppositories or subcutaneous injection can be chosen if a patient suffering from nausea and vomitus. Intravenous injection of metoclopramide 10 mg or dimenhydrinate 62,5 mg can also be chosen.[15]
2. Prophylactic Therapy All medication used as migraine prophylactic therapy can be considered for VM such as propranolol, bisoprolol, flunarizine, and metoprolol. Tricyclic anti-depressants with serotonin increasing property can be prescribed for patients with anxiety comorbidity.[2] Other drugs such as benzodiazepine, selective serotonin reuptake inhibitors (SSRI), pizotifen, dothiepin, lamotrigine, and acetazolamide are reported to have a positive effect on VM. A



Picture 1: Schematic diagram of the connection between the nociceptive pain pathway in migraine and vestibular system[11].

special diet is reported anecdotally as one form of effective behavioural therapy in controlling VM.[16]

Prophylactic therapy is considered for patients suffering more than three episodes of VM in a month, long duration of each spell, interfere daily activity substantially or an episode that cannot be relieved by abortive therapy. The dose recommended for propranolol is 80-240 mg, 50-200 mg for metoprolol, 5-10 mg for bisoprolol or 5-10 mg flunarizine daily. Topiramate 25-100 mg or valproic acid 500-600 mg daily can be considered as an alternative prophylactic therapy.[4]

Patients having more than 15 episodes in a month or more than eight episodes in a day should be managed with 25-100 mg topiramate or 50-150 mg amitriptyline. Lamotrigine 25-100 mg per day is the therapy of choice for patients with dominantly vestibular symptoms in each episode.[4]

Conclusion

VM is a disease with a significant number and has related to significant consequences to a patient's quality of daily life. Even though ICHD-3 has established diagnostic criteria of VM, diagnosing VM is still pose a big challenge to clinicians. VM is a product of genetic vulnerability that increases sensitivity to the interaction between the nociceptive and vestibular tract in our brain. VM is a purely clinical diagnosis. Therefore, anamnesis and neurological diagnosis are the keys to establishing a diagnosis. Treatment of choice for VM is similar to migraines. Zolmitriptan is the first-line drug as abortive treatment. Propranolol, bisoprolol, flunarizine, or metoprolol can be chosen as prophylactic therapy. In the case of anxiety comorbidity, a tricyclic antidepressant can be prescribed to patients as prophylactic therapy.

Conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

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