Vestibular Migraine
前庭偏頭痛

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Vestibular migraine: An update on current understanding and future directions

Tzu-Chou Huang[1,2], Shuu-Jiun Wang[3,4] and Amir Kheradmand[1,5]

Abstract
Background: Vestibular migraine is among the most common causes of recurrent vertigo in the general population. Despite its prevalence and high impact on healthcare cost and utilization, it has remained an under-recognized condition with largely unknown pathophysiology. In the present article, we aim to provide an overview of the current understanding of vestibular migraine.
Methods: We undertook a narrative literature review on the epidemiology, presentations, clinical and laboratory findings, pathophysiology, and treatments of vestibular migraine.
Results: Currently, the diagnosis of vestibular migraine relies solely on clinical symptoms since clinical tests of vestibular function are typically normal, or difficult to interpret based on inconsistent results reported in earlier studies. The challenges related to diagnosis of vestibular migraine lie in its relatively broad spectrum of manifestations, the absence of typical migraine headaches with vestibular symptoms, and its very recent definition as a distinct entity. Here, we highlight these challenges, discuss common vestibular symptoms and clinical presentations in vestibular migraine, and review the current aspects of its clinical diagnosis and evaluation. The concepts related to the pathophysiology and treatment of vestibular migraine are also discussed.
Conclusion: Vestibular migraine is still underdiagnosed clinically. Future studies are needed to address the pathophysiological mechanisms and investigate effective treatment regimens.

Keywords
Vestibular migraine, vestibular, migraine, dizziness, vertigo, headache

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Introduction

Clinicians are no strangers to patients with migraine symptoms and frequent dizziness. As a common neurological disorder, migraine affets about 15% of the general population (1). Dizziness is also a common symptom, accounting for up to 15% of visits in frontline healthcare settings (2,3). Considering the prevalence of both conditions, an overlap in the clinical presentations of vestibular symptoms and migraine may not seem surprising at firt. Several studies, however, have found a close association between dizziness and migraine beyond coincidence (4–15). Dizziness is more common in migraineurs compared with those suffering from other headache subtypes such as tension-type headache, suggesting a pathological link between migraine and dizziness (9,16,17). In some migraine patients, dizziness or vertigo is even more prominent and debilitating than the headache (12). The link between the vestibular symptoms and migraine is also reflet ed by a higher incidence of migraine in patients with recurrent dizzinss who do not fulfil the criteria for other vestibular disorders (18–23). Such clinical

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Associatio of migraine and dizziness/vertigo

- Prosper Ménière (1861) described Ménière syndrome in migraine patients
- In Germany:
  - Lifetime prevalence of migraine: 14%
  - Life time prevalence of vertigo: 7%
  - Co-occurrence of migraine & vertigo: 3.2% [1]
- Significantly more patients with migraine have vertigo than do Pts with TTH and headache-free controls [2,3]
- In some migraine Pts, dizziness / vertigo is even more debilitating than the headache, but does not fulfill the criteria for specific vestibular disorders

[1] Neuhauser Hk, et al. Baillieres Clin Neurol 2006; 67(6):1028–1033
[2] Cutrer FM et al. Migraine-associated dizziness. Headache 1992; 32:300–304
[3] VukovicV, et al. Headache 2007; 47:1427–1435

Vestibular migraine (VM)

- Recurring vestibular symptoms in migraine patients
- a.k.a:
  migraine-associated dizziness
  migrainerelated vestibulopathy
  migrainous vertigo
  benign recurrent vertigo
- It is the commonest cause of spontaneous episodic vertigo

Epidemiology of VM

- Benign paroxysmal vertigo of childhood: 3% (children aged 6–12 yr) [1]
- VM: 2.7% in adults (USA, ICHD-3 criteria) [2]
- Lifetime prevalence: 1%
  One-year prevalence: 1% (Germany) [3]
- In specialized dizziness and headache clinics: 4–10% [4,5]
- In a community-based study of middle-aged women, the 1-year VM prevalence was about 5% [6]

[1] Abu-Arafeh I, et al. Cephalalgia 1995; 15: 22–25
[2] Formeister EJ, et al. Otol Neurotol 2018; 39: 1037–1044.
[3] Neuhauser HK, et al. Neurology 2006; 67: 1028–1033.
[4] Neuhauser H, et al. Neurology 2001; 56: 436–441.
[5] Lempert T, et al. J Neurol 2009; 256: 333–338.
[6] Hsu L-C, et al. Cephalalgia 2011; 31: 77–83.

Demographics of VM

- Female predominance (F/M: 1.5–5)
- Onset of age: 8–50 yr (median age: mid-30s to 40s)
- Usually, migraine headache tends to present first
  Patients may be headache-free for years before the onset of vestibular Sx
- Vestibular Sx can become more pronounced around menopause
- Famililar occurrence has been reported [1]

[1] Lee H, et al. PHeadache 2008; 48: 1460–1467.

Clinical manifestation of VM (1)

- A current or past Hx of migraine
- migraine features must be present >50% of the time along with vestibular symptoms
- photophobia (60–87%), phonophobia (70–86%), migraine aura (13–36%)
- Similar triggers as migraine
- Headache ⟹ vestibular Sx or
  Vestibular Sx ⟹ headache
- Headache & vestibular Sx may never occur together

[1] Neuhauser H, et al. Neurology 2001; 56: 436–441.
[2] Zhang Y, et al. Cephalalgia 2016; 36: 240–248.

Clinical manifestation of VM (2)

- Vestibular Sx: generally triggered or aggravated by changing position, self-motion, or visual motion within the surrounding environment
- Auditory Sx: aural fullness, tinnitus (40%)
- Nonspecific Sx: nausea, vomiting, susceptibility to motion sickness

Table 2. Vestibular symptoms in vestibular migraine patients and relevant terminology defined by the International Classification of Vestibular Disorders (ICVD).

Terms usually used by patients	Vestibular symptoms defined by ICVD
Spinning, rocking, tilting or swaying	Spontaneous vertigo as a false motion sensation of self or surrounding
Unsteady, off-balance or off-kilter	Visually induced vertigo
Lightheaded	Positional vertigo (after a change of head position)
Foggy, clouded or disoriented	Head motion-induced vertigo (during head motion)
Drunk or seasick	Head motion-induced dizziness (sensation of disturbed spatial orientation)
Floating sensation, or walking on air or pillow	
Coming off a roller-coaster or merry-go-round	

Clinical manifestation of VM (3)

- Spontaneous vertigo: internal vertigo (a sensation of self-motion), or external vertigo (a sensation of motion within surroundings) most common
- Positional vertigo (after a change of head position)
- Head motion-induced vertigo (during head motion)
- Head motion-induced dizziness (sensation of disturbed spatial orientation)
- Visually induced vertigo (triggered by complex or large moving visual stimuli)
- These symptoms may vary in individual patients
- Duration: minutes (30%), hours (30 min), days (30%), fluctuating daily Sx (10%).

Clinical overlap of VM manifestation

- Migraine w/ brainstem aura
- BPPV (benign paroxysmal positional vertigo)
- Ménière's disease
- PPPD (persistent postural-perceptual dizziness)

} maybe comorbid with migraine

Diagnostic criteria for VM based on ICHD-3 and ICVD

Vestibular migraine (ICHD-3 and ICVD)

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*
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:
   1. Headache with at least two of the following four characteristics:
      a) Unilateral location
      b) Pulsating quality
      c) Moderate or 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 vestibular disorder

Probable vestibular migraine (ICVD)

A. At least five episodes with vestibular symptoms of moderate or severe intensity, lasting 5 min to 72 hours
B. Only one of the criteria B and D for vestibular migraine is fulfilled (migraine history or migraine features during the episode)
C. Not better accounted for another vestibular or ICHD diagnosis

ICHD-3: International Classification of Headache Disorders, 3rd edition
ICVD: International Classification of Vestibular Disorders of the Bárány Society

Pathophysiology of VM (1)

- The pathophysiology VM has not of been established
- In migraine: altered neural activity within the TVS is considered the primary mechanism for headache
- CGRP & serotonin also expressed in vestibular system
- The nociceptive brainstem centers (NRM, PAG, hypothalamic areas) are also connected with the TVS and vestibular nuclei
- Sensory dysmodulation: exposure to one sensory stimulus results in hypersensitivity that can extend to other sensory stimuli
- Visuospatial symptoms in VM patients are related to altered sensory processing and integration that contribute to the perception of spatial orientation

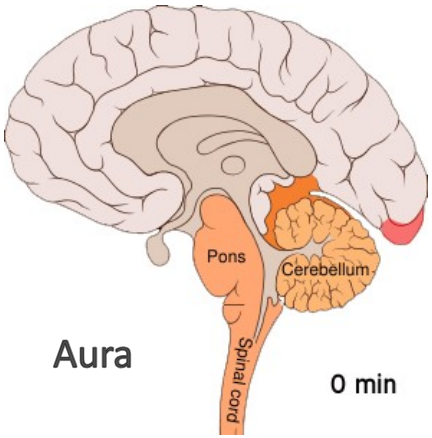
TVS= trigeminovascular system; CGRP = calcitonin gene-related peptide; NRM = nucleus raphe magna; PAG = periaqueductal gray matter

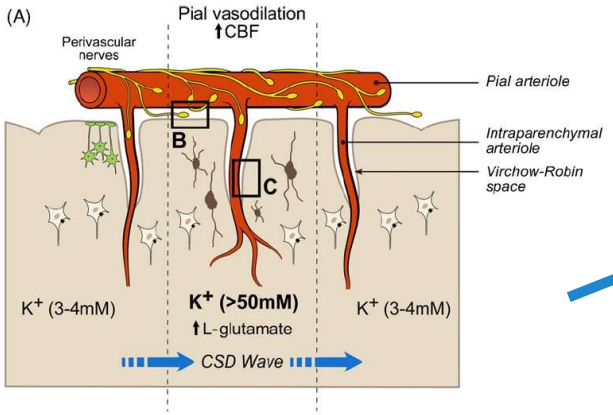
Pathophysiology of VM (2)

- Imaging studies suggest structural and functional changes within the temporo-parietal regions in VM Pts [1]
  ⟹ sensory integration for coherent spatial perception
- VM patients were also found to have abnormal thalamic activities [2]
  - ↑ thalamic activations with cold water ear irrigation during fMRI studies (vs. migraine patients without aura or healthy controls).
  - The magnitude of thalamic activation was positively correlated with the frequency of migraine attacks in VM patients.
- ↑ictal PET activities during vertigo attacks in VM Pts were noted in the temporo-parieto-insular areas and bilateral thalami [1].

[1] Shin JH, et al. Cephalalgia 2014; 34: 58–67.
[2] Russo A, et al. Neurology 2014; 82: 2120–2126.

Proposed pathophysiological mechanisms in the generation of migraine

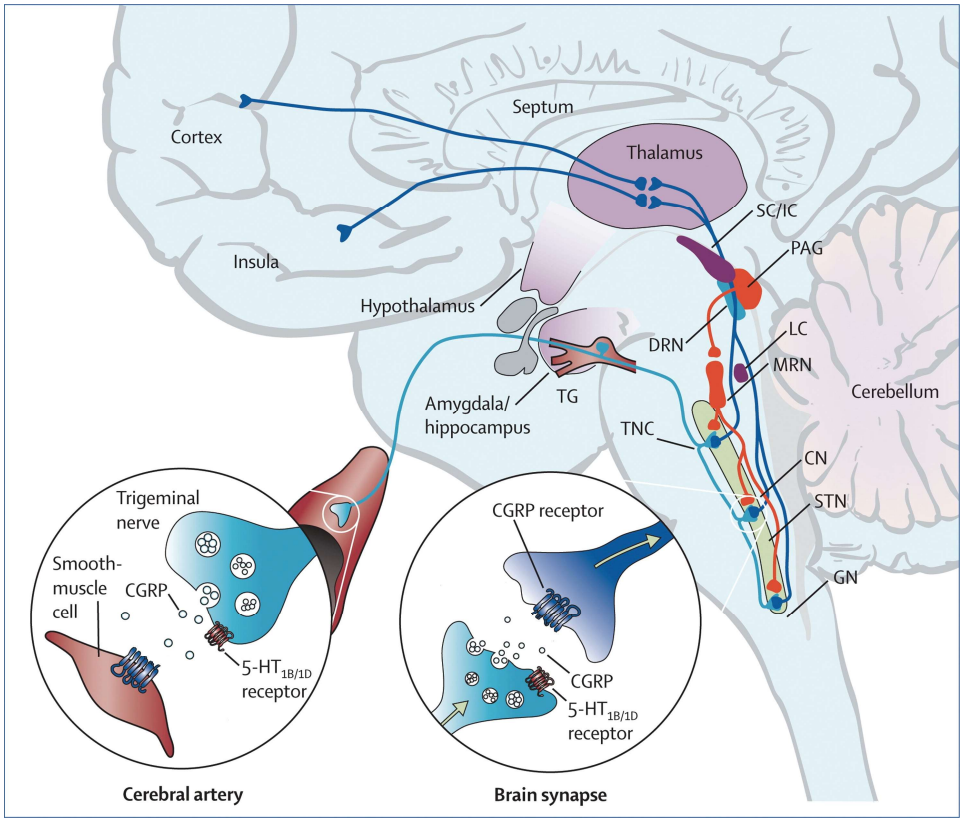




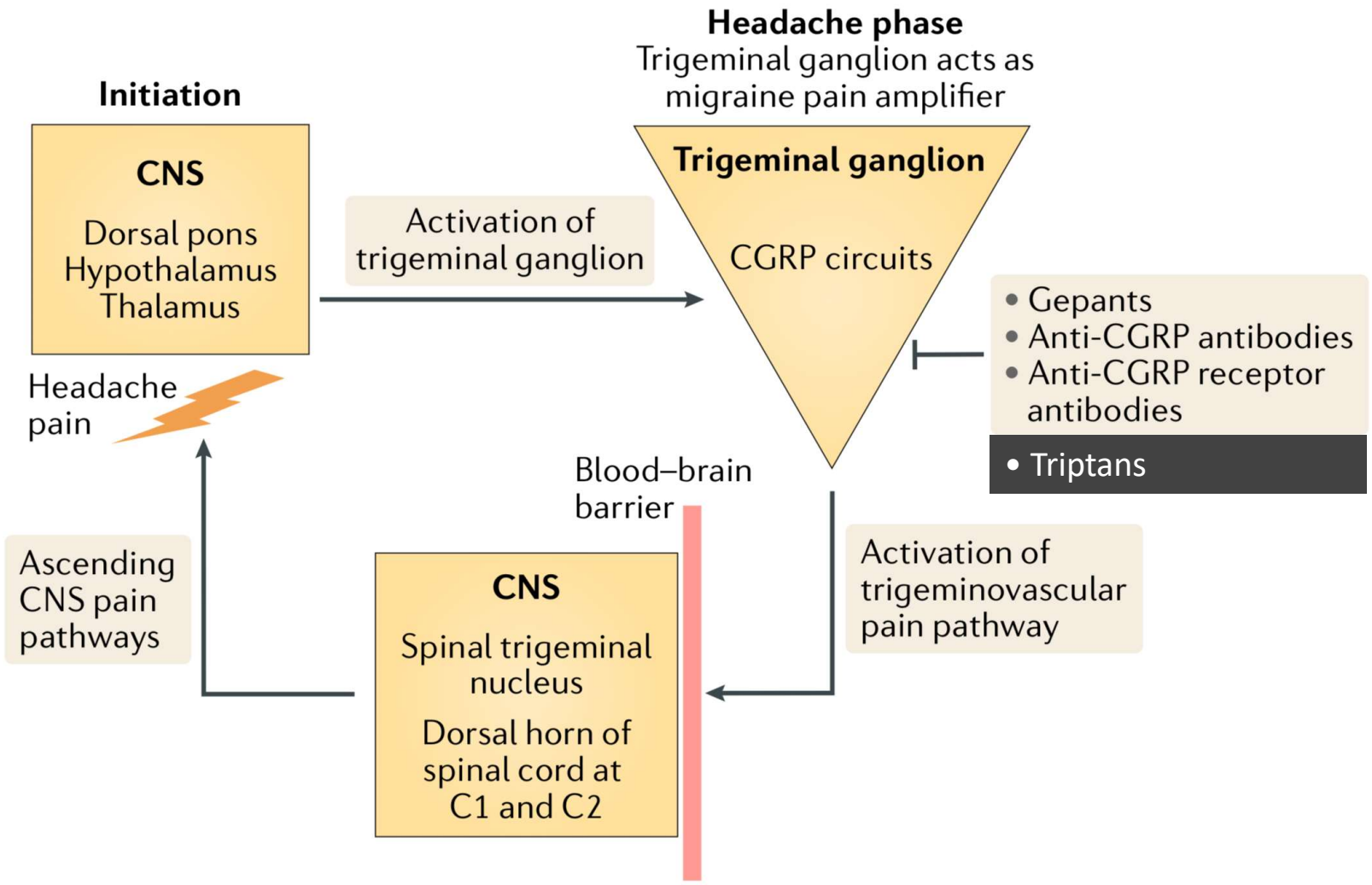
During CSD: The perivascular nerves can release CGRP (also acetylcholine & NO).

In the periphery: **CGRP** release leads to vasodilatation & mast cell degradation.

Progress in Neurobiology 86 (2008) 379-395; Lancet. 2008;372(9656):2089-90.



In brainstem: **CGRP** release facilitate pain transmission.
Abnormal modulation of trigeminocervical neurons (central sensitization) also contributes to migraine pathogenesis.



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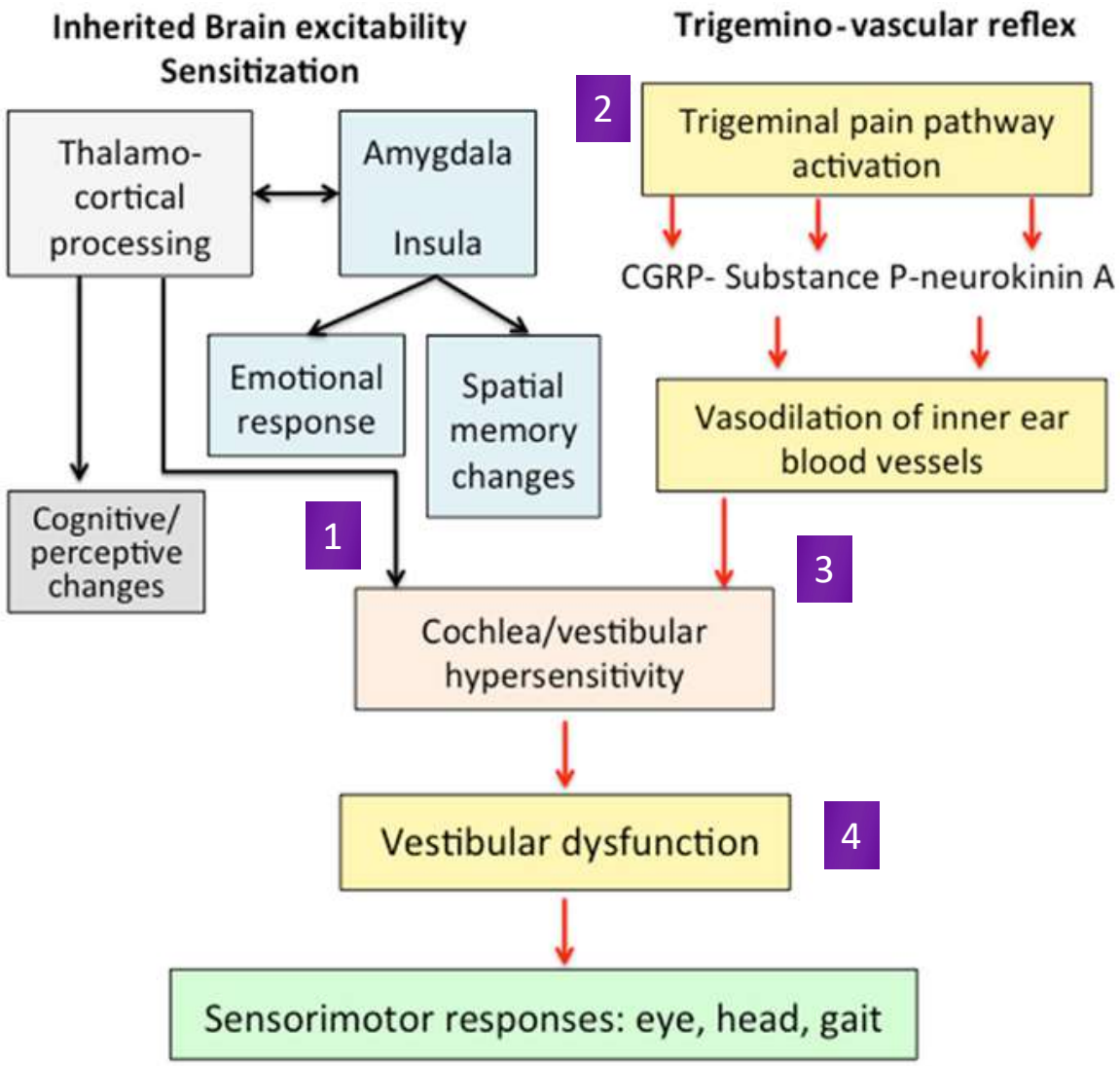


Front Neurol. 2015; 6: 12. Published online 2015 Feb 6. doi: 10.3389/fneur.2015.00012

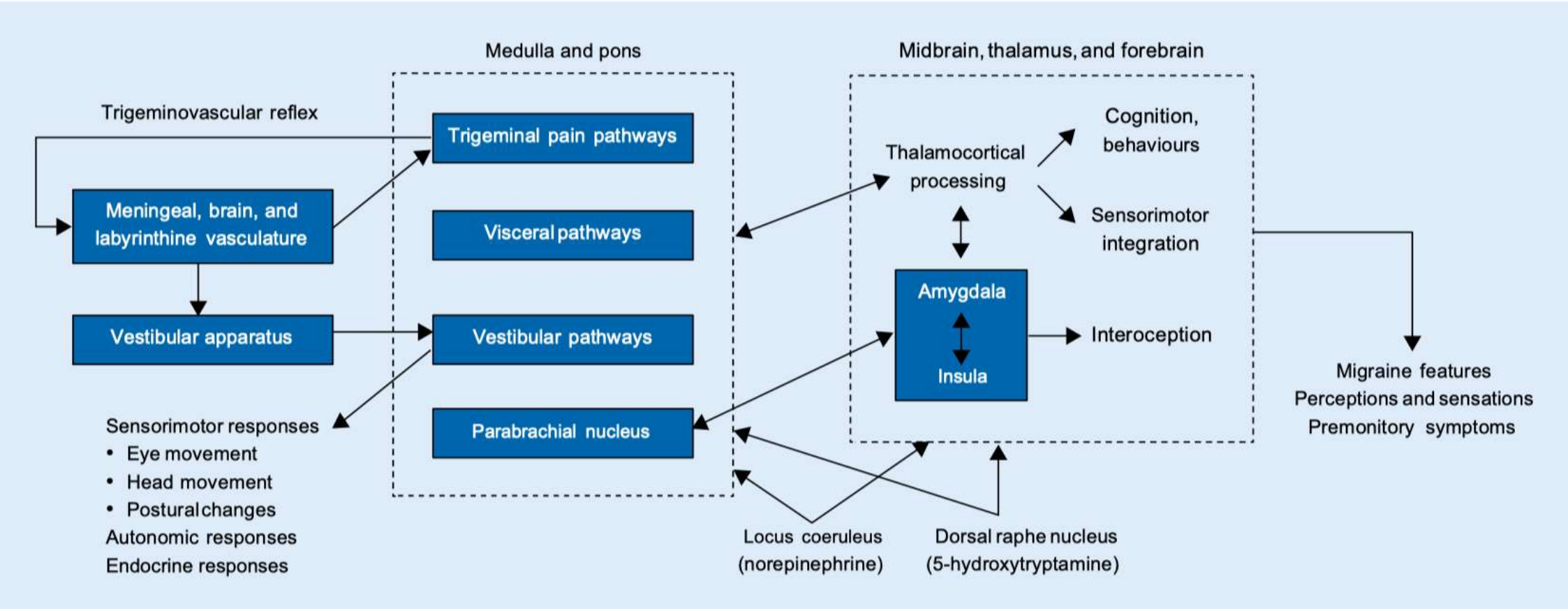
1. Abnormal sensory modulation or integration within the thalamo-cortical network could result in dizziness and spatial disorientation.

2. Hyperactivity within the trigeminovascular system (TVS) and nociceptive brainstem centers could result in headache.

3. Altered activity in the vestibular system could lead to transient vestibulo-ocular dysfunction or vestibular hypersensitivity associated with migraine features.

4. The abnormal processing of vestibular and nociceptive information could determine a transient vestibular dysfunction associated with migraine features.

Pathophysiology of VM (2)



Lapira A. HNO 2019 Jun;67(6):425-428.

Genetics of VM

- The familial occurrence of VM suggests a genetic component in its pathogenesis.
- Lack of evidence for monogenic inheritance
- Polygenic inheritance?

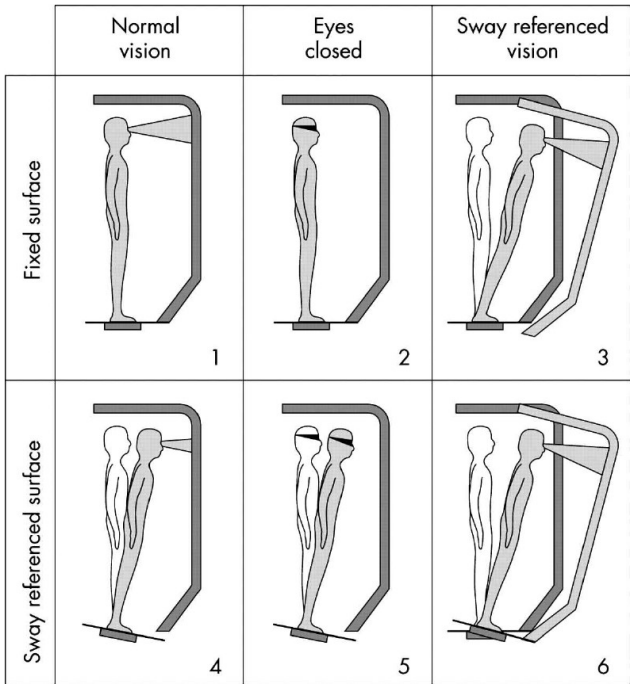
Clinical finding and laboratory testing of VM (1)

- VM is a Dx primarily based on clinical Hx
- N.E. is usually normal in VM Pts during symptom-free periods
- Some mild, non-specific vestibulo-ocular abnormalities could be observed
  - Pursuit abnormality (48%)
  - Central positional* or gaze-evoked nystagmus (28%)
  - Spontaneous nystagmus (10%)
  - Head shaking induced nystagmus⌖

* noted after removal of visual fixation (ie, under Frenzel goggle); low-velocity, sustained during the vestibular attack
⌖ maybe noted during or between the attacks

Clinical finding and laboratory testing of VM (2)

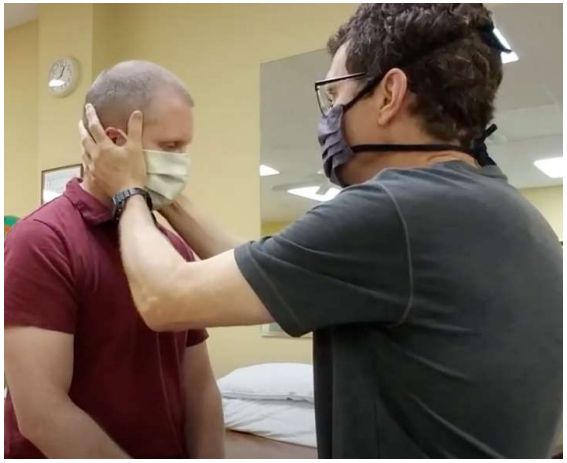
- Balance impairment:
  - commonly VM PTs, such as abnormal Romberg test or sensory organization test
- Static posturography:
  - ↑sway in VM Pts (vs. healthy controls)
- Hearing tests:
  - hearing impairment noted in 8% of VM Pts
  - mild and non-progressive



Clinical finding and laboratory testing of VM (3)

- Vestibular laboratory abnormalities: quite variable among VM Pts
- central vestibular dysfunction?
  peripheral vestibular dysfunction?
- Abnormal findings cannot be specific to VM, and may represent a secondary migraine syndrome triggered by uncompensated vestibular dysfunction
- Nevertheless, vestibular testing is still helpful to r/o other disorders considered in the DDx

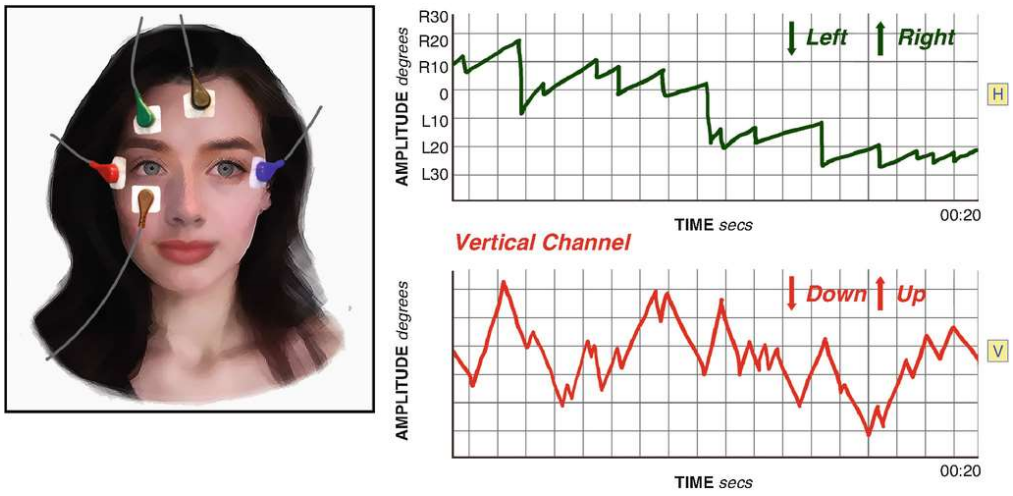
Laboratory diagnostic approach of VM (1)

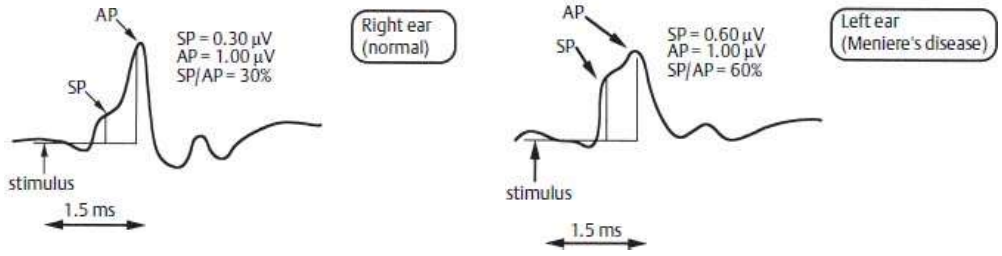


- **High-frequency headshake test**:
  - VM is characterized by dynamically induced motion sensitivity, exhibiting nystagmus enhanced by high-frequency headshake testing
- **Video-oculography (VOG) positioning testing**:
  - 24% of migrainous vertigo patients exhibit positive positional deficits in vertical or horizontal canals

Laboratory diagnostic approach of VM (2)

- **Videonystagmography (VNG)/Electronystagmography (ENG)-Caloric test**
  - 20–25% of Pts with VM have permanent reduced caloric weakness due to the recurrent channelopathies causing peripheral vestibular dysfunction
- **Electrocochleography (ECoG)**:
  - helps to differentiate MD from VM





In active MD, the ratio of the summating potential and the nerve action potential is greater than 35%

Laboratory diagnostic approach of VM (3)

- **The cervical and ocular vestibular evoked myogenic potentials** (cVEMP/oVEMP)
  - The widely used laboratory tests of otolith function
  - Conflicting results in VM Pts.
- **Magnetic resonance imaging** (MRI):
  - to exclude acoustic or CP angle tumors, if patients present with unilateral cochleovestibular symptoms or refractory to treatment

DDx of VM

Table 1
Differential diagnosis of vestibular migraine

Disorder	Key Features
BPPV	Vertigo lasting seconds to 1 min provoked by changes in head position. Positive positional test with typical positional nystagmus (beating most often in a torsional-vertical plane)
Ménière's disease	Spontaneous vertigo lasting 20 min to 12 h with concurrent hearing loss, tinnitus, and aural fullness. Progressive hearing loss over years starting in 1 ear
Vertebrobasilar TIA	Acute attacks lasting mostly minutes, with brainstem symptoms including vertigo, ataxia, dysarthria, diplopia, or visual field defects (but isolated vertigo may also occur). Often associated with craniocervical pain. Usually elderly patients with vascular risk factors
Vascular compression of the eighth nerve	Brief attacks of vertigo (seconds) several times per day with or without cochlear symptoms, typically responsive to carbamazepine
Autoimmune inner ear disease	Frequent attacks of variable duration, often bilateral with rapidly progressing hearing loss
Insufficient compensation of unilateral vestibular loss	Brief and mild spells of vertigo during rapid head movements, oscillopsia with head turns to affected ear. Positive head impulse test to affected side
Schwannoma of the eighth nerve	Rarely presents with (mild) attacks of vertigo. Key symptoms are slowly progressive unilateral hearing loss and tinnitus. Abnormal BAER
Anxiety disorder	Provocation or exacerbation in specific situations (leaving the house, public transport, supermarket), avoidance behavior, often prominent fear of falling

BAER = brainstem auditory evoked response
BPPV = benign paroxysmal positional vertigo
TIA = transient ischemic attack

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Management of VM (1)

- There are few data on VM management, despite its importance in daily practice.
- Some authors recommend treating VM with multiple drugs, while others focus on using only one.
- Rescue medication should be given for rare and long vestibular attacks; frequent episodes require prophylaxis.
- Patients should be referred to a psychiatrist or behavioral therapy should be suggested if psychiatric symptoms are prominent.
- Vestibular rehabilitation therapy should be considered for all patients.

Management of VM (2)

Adjust treatment strategies based on each patient's needs:

- Lifestyle modification: identify the triggers
- Dietary adjustments: avoid triggers (red wine, aged cheeses, artificial sweeteners, processed meats, chocolate, caffeine, MSG, alcohol)
- Medications
- Vestibular physical therapy
- Activities that can enhance perception of spatial orientation (ping-pong or dancing)

Medications for VM: prophylactic treatment (1)

- Anti-HTN, anti-depressants, anti-epileptics are commonly used
  - Beta-blockers: propranolol
  - Calcium channel blockers: flunarizine, cinnarizine, verapamil
  - Anti-depresants: tricyclics, SSRI, SNRI
  - Anti-epileptic: topiramate, valproic acid
  - Acetazolamide
- Others:
  - Botox injection (as add-on)
  - CGRP monoclonal antibody? Ditan (5-HT_{1F} agonist)? Neuromodulation?

Medications for VM: prophylactic treatment (2)

- Effective control should be maintained for at least 1 year and restarted if dizziness recurs on stopping medication.
- Insufficient evidence from randomized controlled trials to verify the effect of these medications for VM

Table 3. Summary of studies on preventive treatments for vestibular migraine defined based on the ICHD-3 criteria.

Drug	Daily dose	Study design	Duration	Outcome	
Propranolol	40–160 mg	33 patients, prospective, randomized, controlled	4 months	Severity: DHI 55.8 ± 2.7 to 31.3 ± 3.7* VSS 7.3 ± 0.3 to 2.1 ± 0.4* Attacks per month: 12.6 ± 1.8 to 1.9 ± 0.7*	(Salviz et al. 2016) (158)
Venlafaxine	37.5–150 mg	31 patients, prospective, randomized, controlled	4 months	Severity: DHI 50.9 ± 2.5 to 19.9 ± 2.9* VSS 7.1 ± 0.3 to 1.8 ± 0.5* Attacks per month: 12.2 ± 1.8 to 2.6 ± 1.1*	(Salviz et al. 2016) (158)
Venlafaxine	37.5 mg	25 patients, prospective	3 months	Severity: DHI 41.7 ± 16.9 to 31.3 ± 14.1* VSS 5.9 ± 1.7 to 3.8 ± 1.2*	(Liu et al. 2017) (157)
Flunarizine	10 mg	25 patients, prospective	3 months	Severity: DHI 46.6 ± 15.1 to 39.8 ± 16.3* VSS 6.4 ± 1.9 to 5.9 ± 1.6*	(Liu et al. 2017) (157)
Valproic acid	1000 mg	25 patients, prospective	3 months	Severity: DHI 46.8 ± 13.5 to 38.7 ± 13.6* VSS 5.8 ± 1.8 to 5.3 ± 1.0	(Liu et al. 2017) (157)
Cinnarizine	75 mg	24 patients, retrospective open-label	3 months	Attacks per month: 3.8 ± 1.1 to 0.4 ± 0.6*	(Taghdiri et al. 2014) (160)

*$p < 0.05$.

DHI: dizziness handicap inventory (175); VSS: vertigo severity score (157,158).

+Model
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ORIGINAL ARTICLE

The effectiveness of propranolol, flunarizine, amitriptyline and botulinum toxin in vestibular migraine complaints and prophylaxis: a non-randomized controlled study☆

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KEYWORDS
Vestibular migraine;
Vestibular migraine treatment;
Botulinum toxin

Abstract
Introduction: Vestibular migraine is the most common cause of spontaneous episodic vertigo in adult patients and the second most common cause of vertigo in patients of all ages.
Objective: To assess the effectiveness of oral medication type (propranolol, flunarizine, and amitriptyline) and botulinum toxin A application on vestibular symptoms, headache severity and attack frequency for vestibular migraine patients.
Methods: Sixty patients with vestibular migraine were enrolled. Thirty patients received botulinum toxin A treatment (B+ group) in addition to the oral medication, whereas 30 patients received only oral medication (B− group). Headache severity was evaluated with Migraine Disability Assessment Scale and vertigo severity was evaluated with Dizziness Handicap Inventory scale. Vestibular migraine attack frequencies in the last three months were also evaluated.
Results: There was a statistically significant decrement in mean Dizziness Handicap Inventory scores, Migraine Disability Assessment Scale scores and vertigo attack frequencies after treatment for all patients, B+ and B− group patients ($p < 0.001$ for all). The mean Migraine Disability Assessment Scale score gains ($p < 0.001$) and vertigo attack frequency

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Both B+ and B− group patients exhibited significant improvement in vestibular migraine attack frequencies, Dizziness Handicap Inventory score and MIDAS (Migraine Disability Assessment Scale) score values.

Botulinum toxin A application had a more pronounced effect for MIDAS (Migraine Disability Assessment Scale) score gain and vestibular migraine attack frequency values, but not for Dizziness Handicap Inventory score gain values.

Thus, botulinum toxin A application should be considered for vestibular migraine patients whose headache severity degrees are more profound.

Görür K, et al. Braz J Otorhinolaryngol 2021 Mar 7;S1808-8694(21)00026-4.

Medications for VM: acute treatment

- Betahistine:
  - a histamine analogue,a classic drug for MD, also relieve the vestibular Sx of migraine
- Triptans:
  - 38% of VM patients improved from severe or moderate vertigo to mild or no vertigo in two hours after taking zolmitriptan, compared to 22% with placebo [1]
  - Rizatriptan reduced vestibular-induced motion sickness in migraineurs compared to the placebo [2]
  - Sumatriptan was also effective in improving both headache and vertigo regardless of their temporal relation [3]
- Steroids
  - effective in 4 patients with prolonged or frequent vertigo attacks in VM Pts [4]

[1] Neuhauser H, et al. Neurology 2003; 60: 882–883.
[2] Furman JM, et al. J Headache Pain 2011; 12: 81–88.
[3] Bikhazi P, et al. Am J Otol 1997; 18: 350–354.
[4] Prakash S, et al. Headache 2009; 49: 1235–1239.

Conclusion

- Vestibular migraine probably represents the second most common cause of vertigo after BPPV, but it remains underdiagnosed clinically.
- The Dx of VM is entirely based on clinical Hx, and no laboratory test is pathognomonic.
- The pathophysiology of VM remains obscure, but recent studies suggest sensory dysfunction is related to processing vestibular inputs.
- The treatment of VM requires lifestyle adjustment, trigger avoidance and vestibular rehabilitation as well as abortive and preventive medications, although solid evidence is still lacking.
- There are still relatively few published reports on vestibular migraine management, despite its enormous importance in daily practice.