Acute spontaneous vertigo in migraineurs: migrainous vertigo or vestibular neuritis?

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When *encounter with a migraineur with acute vertigo with a peripheral type nystagmus, should we consider the other differential diagnosis?*

von Brevern M, Zeise D, Neuhauser H, Clarke AH, Lempert T. Acute migrainous vertigo: clinical and oculographic findings. Brain. 2005 Feb;128(Pt 2):365-74.

2005 von Brevern (ictal phase)

Table 3 *Ocular-motor and vestibulospinal findings during acute MV*

Patient	Nystagmus					VOR deficit	GEN	Saccadic pursuit	Gait ataxia	Romberg test	Findings in the interval
	Upright with fixation	Upright without fixation	Supine	Right ear down	Left ear down						
Central vestibular syndrome											
1	U 4°/s;	U 3°/s	U (A)	–	–	–	–	+ L	+	+	–
2	–	TL 3°/s	TL 3°/s	TL (A)	TL (A)	–	–	–	+	+	–
3	–	R 5°/s	R 25°/s	TR 16°/s	TL 8°/s	–	–	–	–	–	n.a.
4	D 9°/s;	D 5°/s	–	R 5°/s	–	–	–	+ R/L	n.f.	n.f.	Hypoacusis
5	–	TL 6°/s	D 6°/s	–	D 3°/s	–	–	–	+	+	Positional nystagmus, hypoacusis
6	–	–	U 16°/s	TR 14°/s	TL 19°/s	–	–	–	+	+	Hypoacusis
7	–	–	R 7°/s	R 8°/s	L 8°/s	–	–	–	–	–	–
8	–	–	–	–	TL 10°/s	–	–	–	+	+	–
9	–	–	–	–	TL 6°/s	–	–	+ R	+	+	Saccadic pursuit, hypoacusis
10	–	–	–	L (A)	–	–	–	–	–	–	–
Peripheral vestibular syndrome											
11	R 4°/s;	R 15°/s	R 14°/s	R 15°/s	R 15°/s	+ L	–	–	+	+	VOR deficit left
12	R 4°/s;	R 33°/s	R 31°/s	R 33°/s	R 31°/s	+ L	–	–	+	+	n.a.
13	R	R	R	R	R	+ L	–	–	+	+	–
Vestibular syndrome of uncertain origin											
14	–	–	–	–	–	–	–	–	–	–	–
15	–	–	–	–	–	–	–	–	+	+	–
16	–	–	–	–	–	–	–	–	–	+	Romberg +
17	–	–	–	–	–	–	+ L	+ L	+	+	GEN; saccadic pursuit, Romberg +
18	–	–	–	–	–	–	–	–	+	+	–
19	–	–	U 5°/s	–	R 4°/s	–	–	–	–	+	Positional nystagmus as in attack
20	–	R	R	R	R	–	+ L	+ R/L	–	–	GEN; saccadic pursuit

GEN = gaze-evoked nystagmus; U = upward; D = downward; R = rightward; L = leftward; TR = torsional to the patient's right side; TL = torsional to the patient's left side; A = quantification not possible due to artefacts; n.a. = not available; n.f. = not feasible. Note that only main directions of nystagmus are presented.

VM can manefest as unilateral vestibular weakness

- 2003 Waterston J: 2 unilateral vestibular hypofunction (Caloric test) in 16 chronic migraine Pts
- 2008 Celebisoy N: 7 unilateral caloric hypofunction out of 35 MV patients (20%)
- 2009 Lempert: during acute attacks, there may be central spontaneous or positional nystagmus and, less commonly, unilateral vestibular hypofunction
- 2013 Boldingh MI: 10/38 positive HIT, 2/38 spontaneous nystagmus, 6/37 unilateral Caloric w
- 2
- 2018 Lee MH: Caloric CP was pathologic in 15 of 36 (42%) VM. Only 3 of 36 (8%) VM patients had abnormal vHIT results.
- 2018 Wang W: 23/40 showed abnormal caloric test (17 unilateral canal paresis, 6 bilateral weakness), 8/40 abnormal VHIT (3 unilateral VOR gain decline, 5 bilateral)
- 2020 Yilmaz MS: Caloric test was abnormal in 17 (34%) patients with VM, while abnormal gain of the lateral canal was obtained in 9 (18%) VM patients.

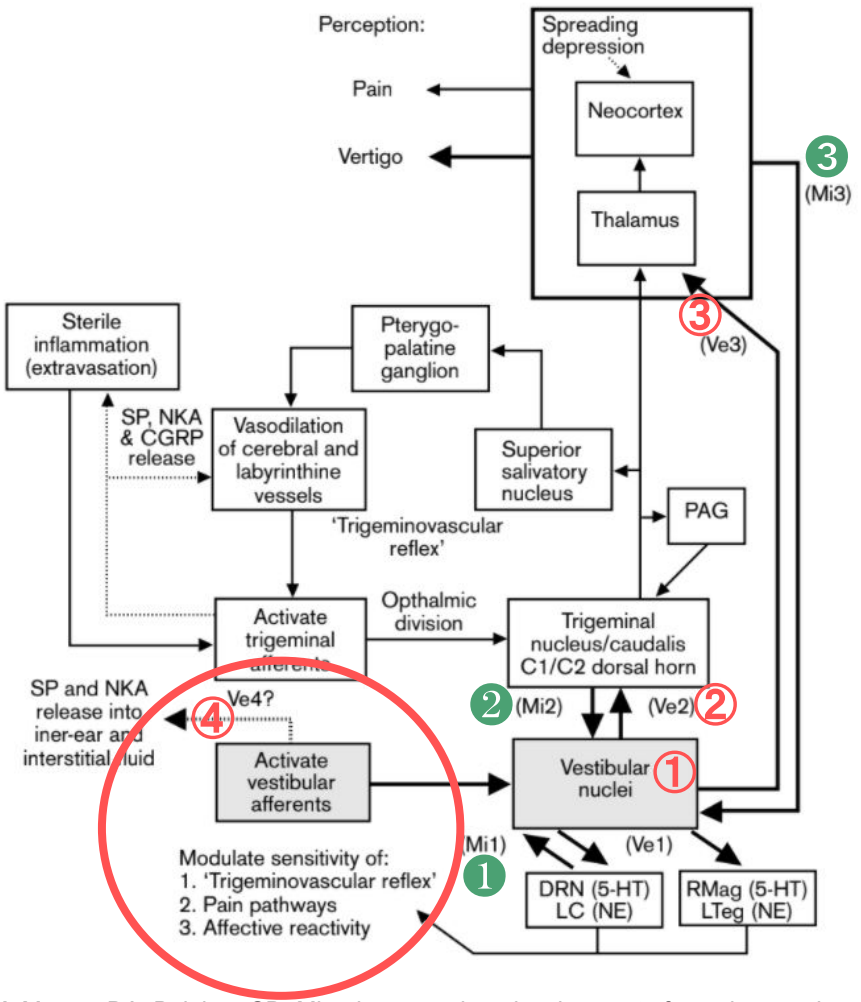
Unilateral vestibular weakness was either diagnosed with spontaneous nystagmus, Caloric paresis, or positive v-HIT (or bedside HIT)

What *is the differences between migrainous vertigo or vestibular neuritis?*

Vestibular migraine

Pathophysiology of migraine

- Central actions of serotonin (from the dorsal raphe nucleus and nucleus raphe magnus) and norepinephrine (from locus coeruleus)
- A trigeminal sensory–parasympathetic reflex (mediated by direct spinal trigeminal nucleus–superior salivatory nucleus connections)
- Direct vasodilator effects of neurokinin A, calcitonin gene-related peptide, and substance P release from trigeminal sensory terminals
- Protein extravasation (sterile inflammatory response) into dura from the same vasoactive peptide release
- A cortical spreading depression-like mechanism for auras



Furman JM, Marcus DA, Balaban CD. Migrainous vertigo: development of a pathogenetic model and structured diagnostic interview. Curr Opin Neurol. 2003 Feb;16(1):5-13.

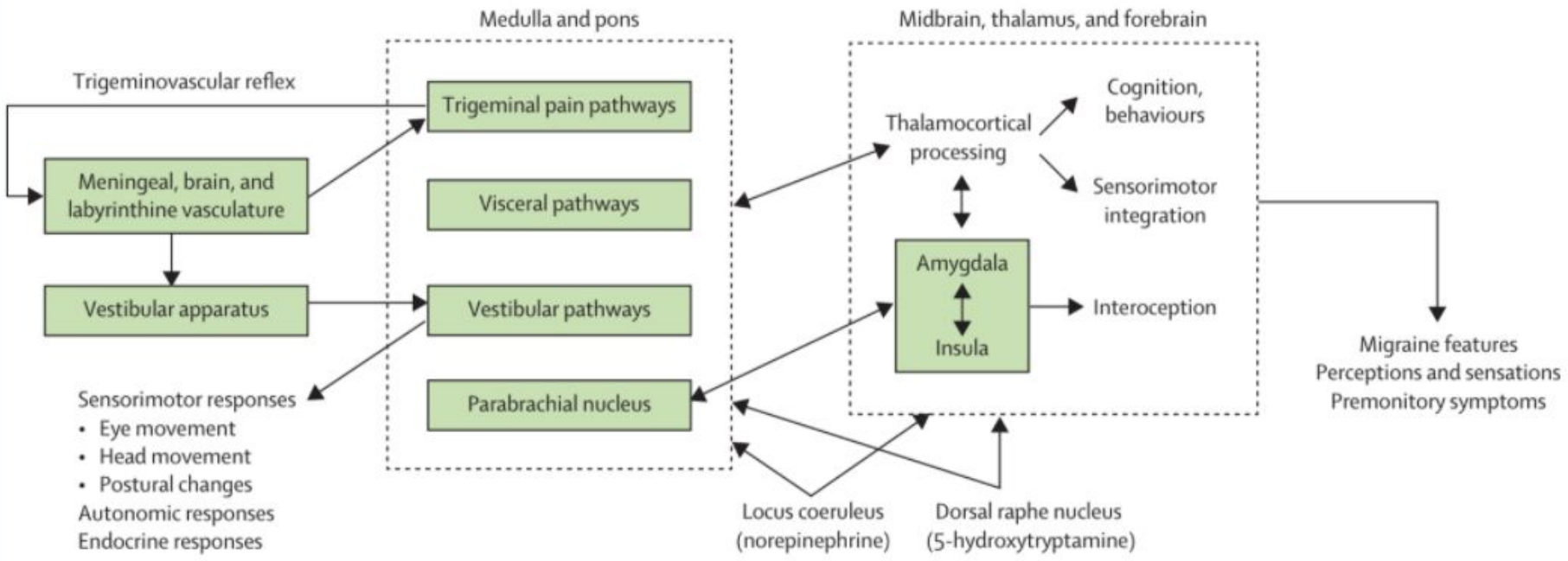
Possible pathophysiology of vestibular migraine

- Spreading depression: short attacks
- Neurotransmitters (calcitonin gene–related peptide, serotonin, noradrenaline, and dopamine): modulate the activity of central and peripheral vestibular neurons
- Connections between the trigeminal and vestibular systems
- Dysfunction of ion channels: FHM type 1/EA 2
- Endolymphatic hydrops

Lempert T, von Brevern M. Vestibular Migraine. Neurol Clin. 2019 Nov;37(4):695-706.

Vestibular migraine

- Overlap between migraine pathways and vestibular pathways



Furman JM, Balaban CD. Vestibular migraine. Ann N Y Acad Sci. 2015 Apr;1343:90-6.

Vestibular migraine

- Despite the availability of diagnostic criteria for vestibular migraine, **uncertainty** remains regarding neurologic localization, underlying pathophysiology, functional balance implications, and management.
- Although diagnostic criteria for vestibular migraine have been formulated, vestibular migraine can have **various clinical presentations**, both between patients and for individual patients over time

Furman JM, Balaban CD. Vestibular migraine. Ann N Y Acad Sci. 2015 Apr;1343:90-6.

Symptoms of vestibular migraine

Diagnostic criteria: at least 5 episodes with **vestibular symptoms** of moderate or severe intensity, lasting 5 min to 72 hours

- Spontaneous vertigo
  - internal vertigo and external vertigo
- Positional vertigo
- Visually-induced vertigo
- Head motion-induced vertigo
- Head motion-induced dizziness with nausea

Lempert T, Olesen J, Furman J, Waterston J, Seemungal B, Carey J, Bisdorff A, Versino M, Evers S, Newman-Toker D. Vestibular migraine: diagnostic criteria. J Vestib Res. 2012;22(4):167-72.

Neuro-otological signs during vestibular migraine

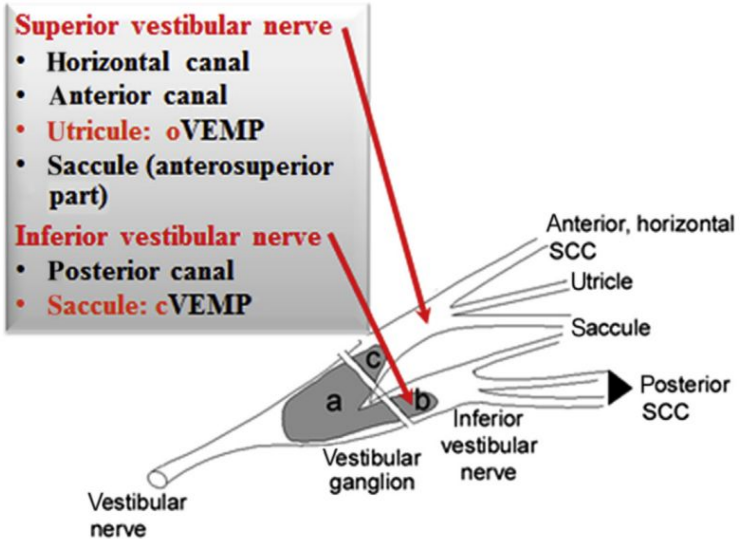
- 1984 Kayan and Hood, migraine, during attack
  - Dysfunction of the vestibular and/or cochlear systems: 77.5%
  - 18.8% central, **28.8% peripheral**, 30% inconclusive
- 1999 Dieterich M
  - Central origin in 14%, **peripheral in 7.5%**, and indetermediate in 17.5%
- 2005 von Brevern
  - 6/20 (30%) isolated spontaneous nystagmus, 5/20 (25%) isolated positional nystagmus, 3/20 (15%) combination
  - Central vestibular dysfunction: 10/20 (50%), **peripheral 3/20 (15%)**, undetermined 7/20 (35%)

Vestibular migraine can have various clinical presentations, including central, peripheral or undetermined signs and symptoms.

Vestibular neuritis

Vestibular neuritis

- 3rd most common peripheral vestibular disorder
- 2015, Strupp: **acute unilateral peripheral vestibulopathy (AUPVP)**
- Most commonly associated with HSV-1 reactivation
- Pathophysiology:
  - Normal end organ: equal resting-firing frequency of the axons
  - Pathologic process: reduction of firing frequency
- Often affects the superior division
  - **Horizontal-rotatory** with a upward component
- Total (superior + inferior)
  - Horizontal nystagmus with torsional nystagmus with no vertical component



Strupp M, Magnusson M. Acute Unilateral Vestibulopathy. Neurol Clin. 2015 Aug;33(3):669-85, x.

Vestibular neuritis

- Diagnosis:
  - History, clinical examinations (laboratory exam in unclear case)
  - A diagnosis of exclusion
- Key signs and symptoms:
  - An acute onset of spinning vertigo, postural imbalance and nausea
  - A horizontal rotatory nystagmus beating towards the non-affected side, with variable vertical component
  - A pathological head-impulse test
  - No evidence for central vestibular or ocular motor dysfunction

Strupp M, Magnusson M. Acute Unilateral Vestibulopathy. Neurol Clin. 2015 Aug;33(3):669-85, x.

Vestibular neuritis - laboratory tests

- Caloric tests:
  - ((R30 + R44) - (L30 + L44))÷((R30 + R44) + (L30 + L44)) (x100%)
  - Vestibular paresis is usually defined as >25% asymmetry
  - Horizontal canal -> inferior vestibular neuritis Caloric會正常
- v-HIT:
  - High frequency of VOR, 6 canals
  - Superior division, inferior division, and total unilateral vestibulopathy patterns
- VEMP
  - cVEMP: saccule/inferior vestibular nerve
    ➔ preserved in 2/3 patients (isolated superior vestibular nerve involvement)
  - oVEMP: utricle/superior vestibular nerve
    ➔ reduced or absent in superior or total vestibular nerve involvement

Strupp M, Magnusson M. Acute Unilateral Vestibulopathy. Neurol Clin. 2015 Aug;33(3):669-85, x.

Why *should VM presented with unilateral vestibular weakness be distinguished from VN (AUPVP)?*

Treatment strategy and response differs between the 2 diagnosis.

Treatment efficacy of VM - acute

- Triptans
  - 2010 Ahn SK: inner ear, 5-HT(1B) and 5-HT(1D) receptor immunopositivity with endothelial cells of the vestibular ganglion, spiral ganglion, vestibulocochlear nerve, spiral ligament and stria vascularis → triptans may be effective

Agent	Evidence	Dosing	Outcome
Almotriptan	Retrospective cohort [39••] $n = 18$	12.5 mg PO within 1 h of attack	Complete vertigo resolution in 55%, > 50% reduction of vertigo in 28%
Sumatriptan	Retrospective Cohort [40••] $n = 53$	PO or IM, dose not specified	Efficacy rating for headache 4, for vertigo 3 (1–4)
Zolmitriptan	Randomized, double-blind placebo-controlled [41••] $n = 10$	2.5 mg PO during attack	Vertigo improvement: 38% at 2 h vs. 22% with placebo

2017 Lauritsen CG, Marmura MJ. Current Treatment Options: Vestibular Migraine. Curr Treat Options Neurol. 2017 Sep 30;19(11):38.

Treatment efficacy of VM - preventive, rehab

- Preventive treatment
  - 2009 Baier B: prophylactic therapy decrease frequency (80%), duration (65%), intensity (68%)
  - 2020 Byun YJ (systematic Review and meta-analysis): vestibular rehabilitation, SNRI, BB, AED, and CCB reductions in DHI
  - 2020 Çelik O: Propranolol reduced severity, frequency, and number of attacks and disability scores, and improved the quality of life
- Vestibular rehabilitation
  - 2020 Byun YJ (systematic Review and meta-analysis): improvement in all parameters, without superiority over pharmacologic agent, more pronounced with longer follow-up

Treatment efficacy of VM - preventive

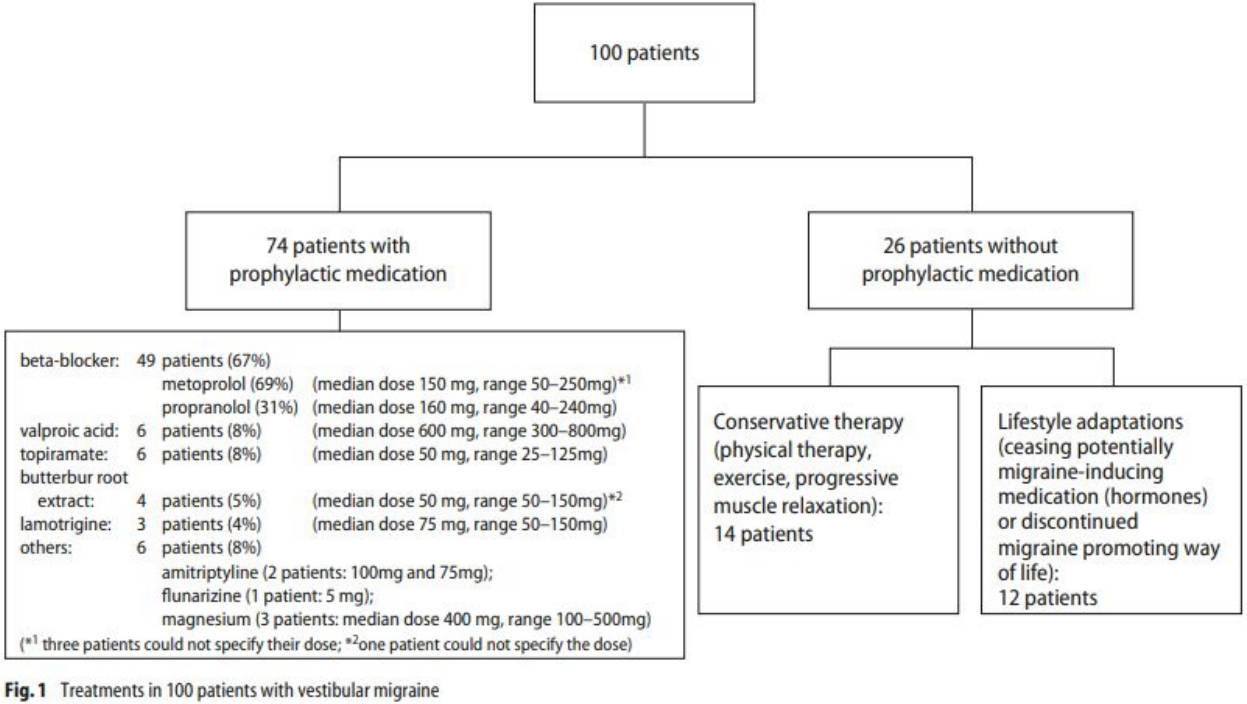
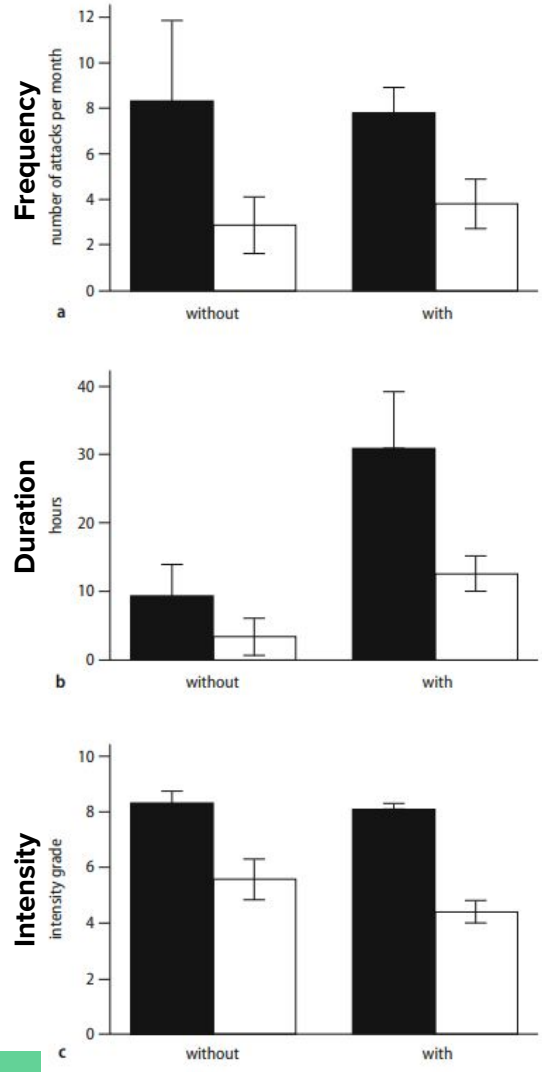


Fig. 1 Treatments in 100 patients with vestibular migraine



Baier B, Winkenwerder E, Dieterich M. "Vestibular migraine": effects of prophylactic therapy with various drugs. A retrospective study. J Neurol. 2009 Mar;256(3):436-42.

Treatment efficacy of VN/AUPVP - acute

- Symptomatic medications:
  - Should only be used in the very early and symptomatic stages of the disorders
- Steroid:
  - 2004 Strupp M: Methylprednisolone significantly improves the recovery of peripheral vestibular function in patients with vestibular neuritis, whereas valacyclovir does not.

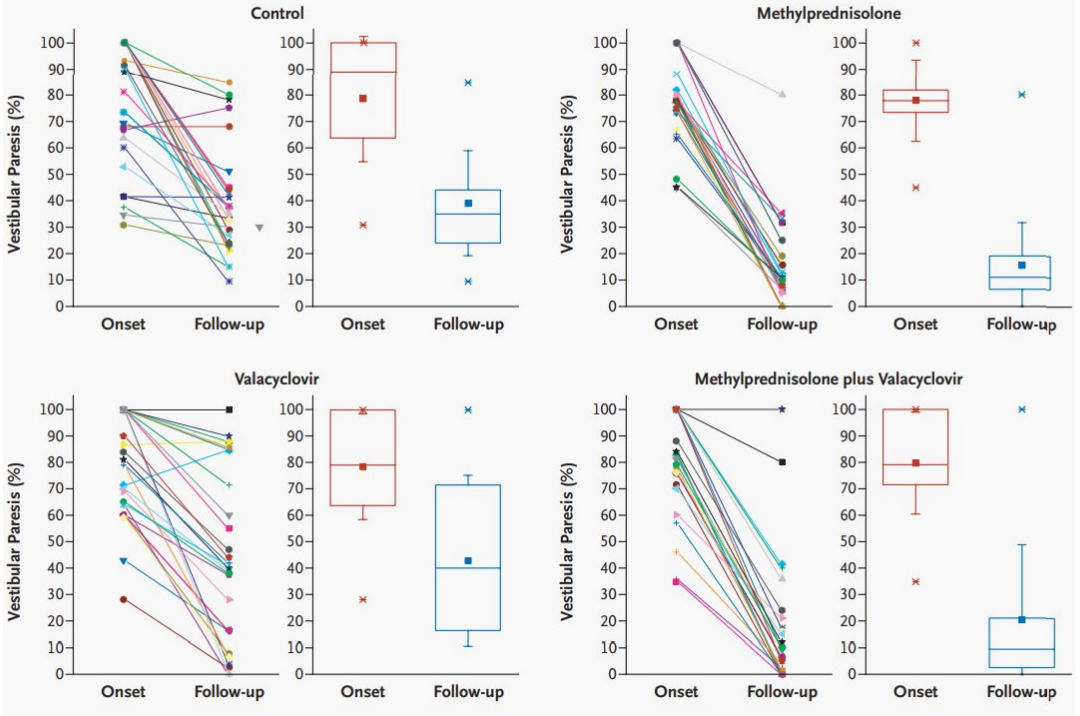


Figure 1. **Unilateral Vestibular Loss within Three Days after the Onset of Symptoms and after 12 Months.**

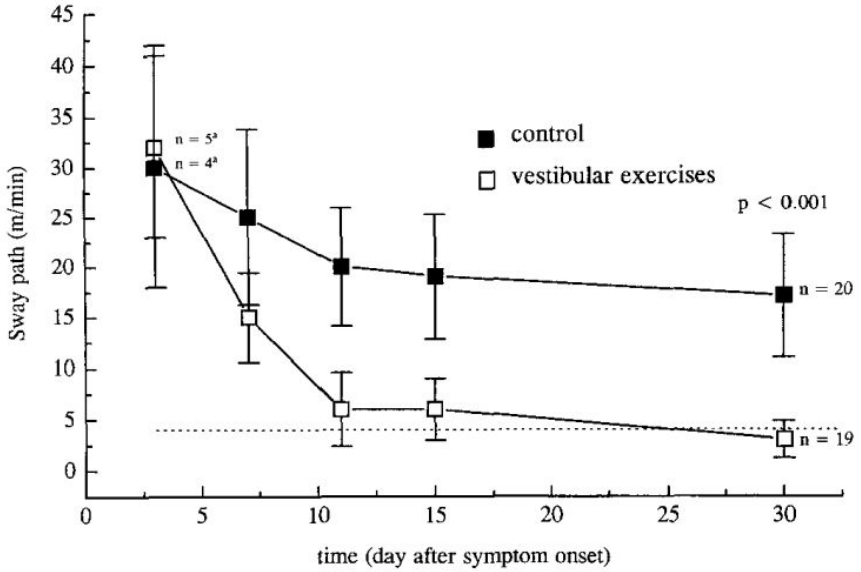
2004 Strupp M, Zingler VC, Arbusow V, Niklas D, Maag KP, Dieterich M, Bense S, Theil D, Jahn K, Brandt T. Methylprednisolone, valacyclovir, or the combination for vestibular neuritis. N Engl J Med. 2004 Jul 22;351(4):354-61

Treatment efficacy of VN/AUPVP - acute

- Steroid:
  - 2010 Goudakos JK: currently available evidence (4 trials), corticosteroids improve only the caloric extent and recovery of canal paresis, not clinical recovery (DHI)
  - 2015 Batuecas-Caletrío A: glucocorticoids may accelerate vestibular compensation via a restoration of peripheral vestibular function (DHI on admission to hospital and just prior to hospital discharge)
  - 2019 Bronstein AM: long-term prognosis is not dependent on the magnitude of the peripheral residual damage (caloric or video head-impulse test). Instead, a combination of visuovestibular psychophysical factors (visual dependence), psychological traits and dysfunctional vestibular perception are relevant.

Treatment efficacy of VN/AUPVP - rehab

- Vestibular rehabilitation:
  - 1998 Strupp M: specific vestibular exercises improve vestibulospinal compensation in patients with acute peripheral vestibular lesions
  - 2017 Crane BT: adaptive vestibular rehabilitation technique, 4 patients with unilateral vestibular hypofunction, symptomatic for at least 3m, DHI 32 to 56 (mean = 42) reduced to 0 to 16 (mean = 11.5) after a month of therapy



How *to distinguish VM with unilateral vestibular weakness from VN (AUPVP)?*

Some comparisons between VM and VN

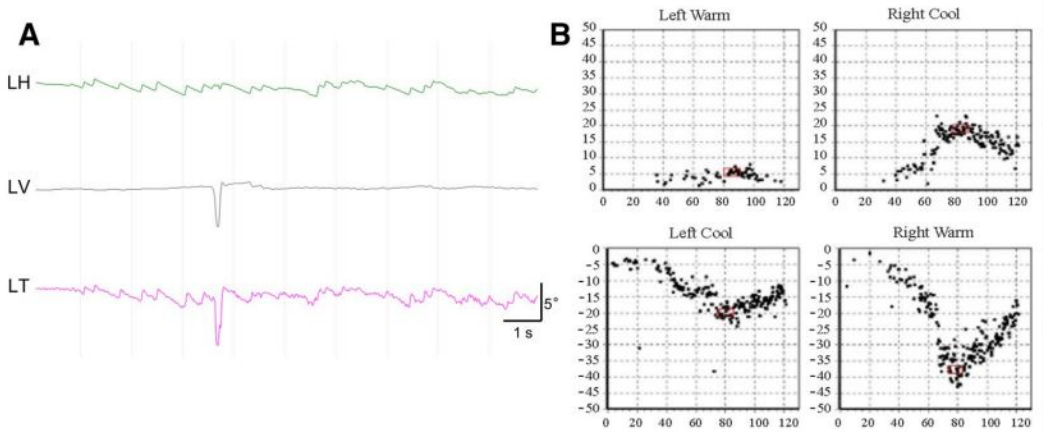
- 2016 Yoo MH:
  - Caloric CP: 23/23 acute VN, 15/23 (65%) in compensated VN, 15/36 (42%) in VM
  - Abnormal vHIT: 20/23 (87%) acute VN, 17/23 (74%) compensated VN, 3/36 (8%) VM
- 20
  -
  - ness)
- **A trend of more pronounced caloric/vHIT abnormalities in VN patients.**
  When it comes to a specific case, still could not differentiate VN/VM with Caloric/vHIT.

	Caloric		vHIT	
2016 Yoo MH	VN 23/23 (100%)	VM 15/36 (42%)	VN 20/23 (87%)	VM 3/36 (8%)
2018 Wang W	VN 45/45 (100%)	VM 23/40 (58%)	VN 35/45 (78%)	VM 8/40 (20%)

Na S, Lee ES, Lee JD, Sung KB, Lee TK. Video head impulse findings in the ictal period of vestibular migraine. J Neurol. 2019 Jan;266(1):242-244. doi: 10.1007/s00415-018-9088-0. Epub 2018 Oct 19.

A case report

- A 40-year-old man presented with positional (sitting up) vertigo without auditory symptoms. He had episodes of vertigo attack followed by a migrainous headache over a 4-year period. This vertigo were quite similar to previous recurrent attacks.
- NE: spontaneous RBN and torsional (clockwise); Bedside HIT: unremarkable; positional maneuver: augmented spontaneous; bow test: down-beating component; lean test: reversed nystagmus (leftward, upward, and torsional (counterclockwise)); horizontal head shaking: augmented spontaneous.
- v-HIT: left HC/PC: early acceleration and premature deceleration (EAPD) -> left HC/PC hypofunction



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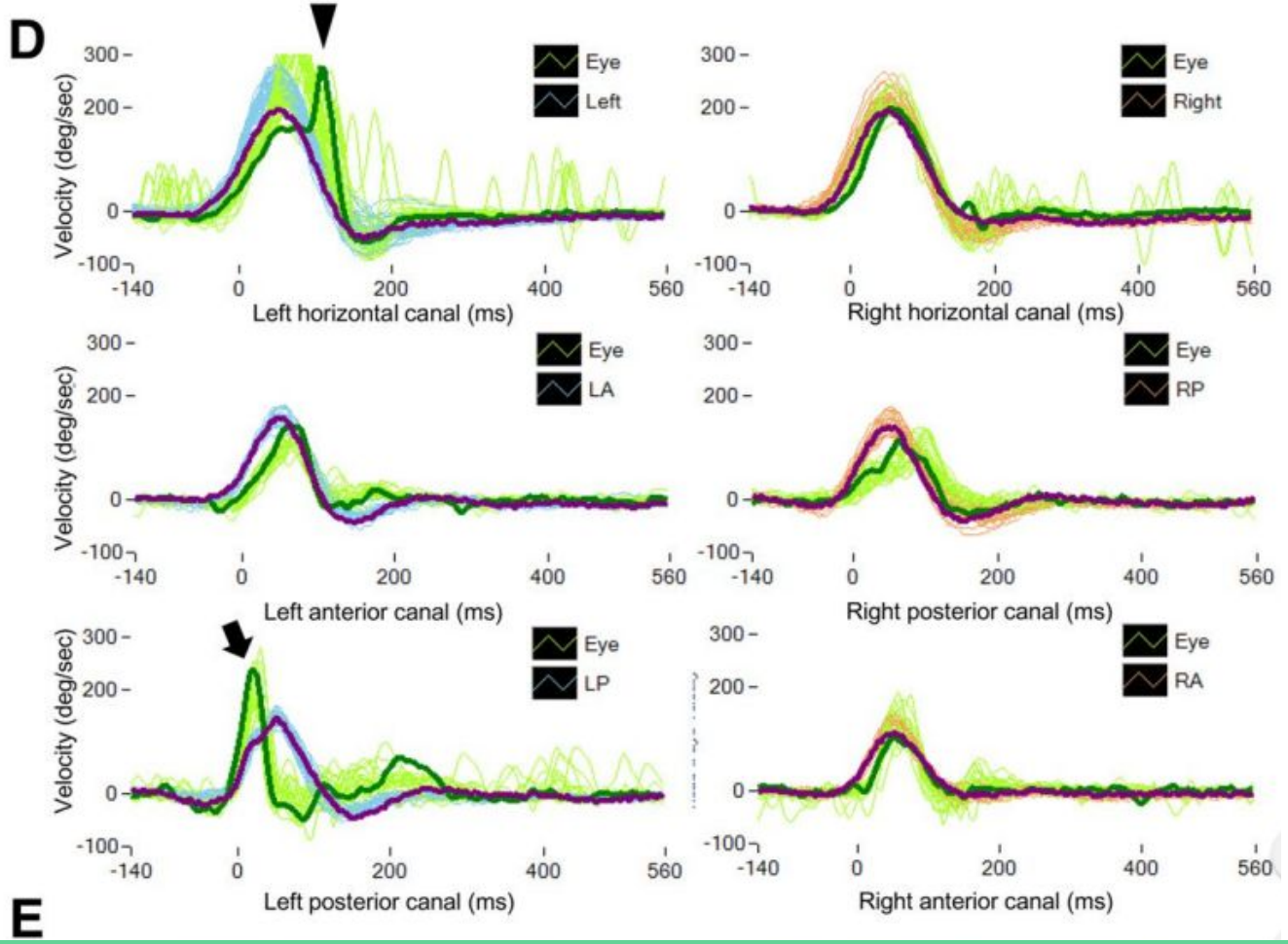

Our suggestions

- A careful clinical history:
  - A history similiar to prior attack may be helping
- A detailed neurological examination may showed subtle signs
  - Vestibular migraine attacks may showed central positional nystagmus in positional tests, while nystagmus in vestibular neuritis doesn’t change directions in positional tests
- Laboratory tests may be helping
  - v-HIT including 6 canals may be conclusive (ex: a pattern compatible with superior devision involvement)
  - Gain assymetry less pronounce in VM
  - Early acceleration and premature deceleration (EAPD) suggests VM
- Drug trials
  - Triptans? Preventive medications?
- Follow up
  - VN/AUPVP may have some remaining vestibular weakness throughout time

Take home message

- Acute spontaneous vertigo in migraineurs should differentiate VM presenting unilateral vestibular weakness with vestibular neuritis.
- Treatment varies in these 2 different diagnosis, proper diagnosis may potentially improve the clinical outcome.
- A careful clinical history, a detailed neurological examination with subtle signs, laboratory tests (ex: v-HIT pattern), drug trials, follow up ➜ may help diagnosis.

Future expectations

When a migraineur came in to our clinic with spontaneous nystagmus

- v-HIT:
  - Complete 6 canals: 看是否符合superior/inferior devision pattern
  - Analysis gain asymmetry: 預期VN較明顯，VM較不明顯，找出cutoff
- VNG:
  - Slow phase velocity (spv, °/s) of nystagmus: 看可否找出cutoff
- Caloric
- VEMP:
  - oVEMP, cVEMP看是否符合superior/inferior devision pattern, correlate with vHIT