

# Journal Pre-proof

Analysis of Video Head Impulse Test Saccades Data in Patients with Vestibular Migraine or Probable Vestibular Migraine

Yi Du, Xingjian Liu, Lili Ren, Yu Wang, Ziming Wu



PII: S1672-2930(22)00036-8

DOI: <https://doi.org/10.1016/j.joto.2022.06.002>

Reference: JOTO 264

To appear in: *Journal of Otolaryngology*

Received Date: 28 March 2022

Revised Date: 9 June 2022

Accepted Date: 10 June 2022

Please cite this article as: Du, Y., Liu, X., Ren, L., Wang, Y., Wu, Z., Analysis of Video Head Impulse Test Saccades Data in Patients with Vestibular Migraine or Probable Vestibular Migraine, *Journal of Otolaryngology*, <https://doi.org/10.1016/j.joto.2022.06.002>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© [copyright Year] PLA General Hospital Department of Otolaryngology Head and Neck Surgery.  
Production and hosting by Elsevier (Singapore) Pte Ltd. All rights reserved.

## Analysis of Video Head Impulse Test Saccades Data in Patients with Vestibular Migraine or Probable Vestibular Migraine

Yi Du <sup>a,b,c,d</sup>; Xingjian Liu <sup>a,b,c,d</sup>; Lili Ren <sup>a,b,c,d</sup>; Yu Wang <sup>a,b,c,d</sup>; Ziming Wu <sup>a,b,c,d\*</sup>;

a. College of Otolaryngology Head and Neck Surgery, Chinese PLA General Hospital, Chinese PLA Medical School, 28 Fuxing Road, Beijing, China

b. National Clinical Research Center for Otolaryngologic Diseases, Beijing, China

c. State Key Lab of Hearing Science, Ministry of Education, Beijing, China

d. Beijing Key Lab of Hearing Impairment Prevention and Treatment, Beijing, China

\* Corresponding author: Ziming Wu (email: [zimingwu@126.com](mailto:zimingwu@126.com); Tel:86-13717658922; Add: College of Otolaryngology Head and Neck Surgery, Chinese PLA General Hospital, 28 Fuxing Road, Haidian District, Beijing, 100853 China)

### ORCID:

Yi Du 0000-0002-0276-0850

Ziming Wu 0000-0003-3635-6482

**Financial disclosures/conflicting Interests:** The authors received no financial support for the research, authorship, and/or publication of this article. The authors declare that they have no conflicts of interest, financial, or otherwise.

## Analysis of Video Head Impulse Test Saccades Data in Patients with Vestibular Migraine or Probable Vestibular Migraine

### Abstract:

**Objective:** Saccades accompanied by normal gain in video head impulse tests (vHIT) are often observed in patients with vestibular migraine (VM). However, they are not considered as an independent indicator, reducing their utility in diagnosing VM. To better understand clinical features of VM, it is necessary to understand raw saccades data.

**Methods:** Fourteen patients with confirmed VM, 45 patients with probable VM (p-VM) and 14 age-matched healthy volunteers were included in this study. Clinical findings related to spontaneous nystagmus (SN), positional nystagmus (PN), head-shaking nystagmus (HSN), caloric test and vHIT were recorded. Raw saccades data were exported and numbered by their sequences, and their features analyzed.

**Results:** VM patients showed no SN, PN or HSN, and less than half of them showed unilateral weakness (UW) on caloric test. The first saccades from lateral semicircular canal stimulation were the most predominant for both left and right sides. Neither velocity nor time parameters were significantly different when compared between the two sides. Most VM patients (86%) exhibited small saccades, around 35% of the head peak velocity, with a latency of 200 - 400 milliseconds. Characteristics of saccades were similar in patients with p-VM. Only four normal subjects showed saccades, all unilateral and seemingly random.

**Conclusions:** Small saccades involving bilateral semicircular canals with a scattered distribution pattern are common in patients with VM and p-VM.

**Keywords:** vestibular migraine; probable vestibular migraine; video head impulse test; saccade; data analysis

### 1. Introduction:

Vestibular migraine (VM) is a common episodic vestibular disorder. There is no definitive test for VM, making it challenging to diagnose. The symptoms of this disorder may vary depending on its stage. During the ictal period, spontaneous and persistent positional nystagmus can be observed [1, 2, 3]. It has been reported that head-shaking nystagmus occurs during interictal periods [4, 5]. Most patients with VM have normal vestibular function tests when in symptom-free stages [6, 7].

Although the video head impulse test (vHIT) is routinely used in vertigo clinics worldwide, abnormal vHIT findings in VM are rarely reported. In vHIT, vestibular dysfunction is generally identified by the vestibular-ocular reflex (VOR) gain loss and evident saccades, whereas subtle saccades with normal gain are usually overlooked. As a ratio directly indicates vestibular abnormality, gain is more useful than saccades [8]. Nevertheless, this measurement is less sensitive than caloric test, and decreased vHIT gains are reported in only 9-11% of VM patients [9, 10]. Qualitatively, saccades are often characterized as overt, covert or combined based on the latency [11]. It seems unlikely that such characterization would be able to provide a quantitative evaluation of vestibular function, although saccades are frequently observed in VM patients [6, 12]. This may be because previous studies only compared VOR

gain [10] without analyzing saccadic findings.

PR score, a recently proposed saccade time variation parameter, may indicate vestibular recovery status [13, 14]. Saccades can be independently measured this way. Despite this, the PR score cannot be used to calculate unapparent saccades (velocities less than  $65^\circ/\text{s}$ ), which may reduce its sensitivity in identifying VM patients. Therefore, an in-depth analysis of saccades data from VM patients, especially those subtle ones, is needed.

Saccades may provide clinicians with a better understanding of VM, in which vestibular test results may not be as normal as once believed. This study compares saccades data between VM patients (including those with probable VM [p-VM]) and normal controls to see if saccades are more sensitive indicators of VM and should be included in the screening vestibular test battery for episodic vestibular disorders. Saccades included in this study were not filtered by a strict boundary and may reflect raw saccades observed in vHIT reports.

## **2. Materials and Methods**

### **2.1 Subjects**

Data from vertigo patients seen at the vertigo clinic, Chinese PLA General Hospital, between July 2020 and November 2021, including 17 that met the diagnostic criteria for VM and 61 for p-VM [15], were retrospectively reviewed. Age-matched healthy volunteers ( $n=14$ ) were also recruited. Ethics approval was obtained from the Chinese PLA General Hospital ethics committee. Vestibular test results, including spontaneous nystagmus (SN), positional nystagmus (PN), head-shaking nystagmus (HSN) and caloric test (unilateral weakness, UW), were documented during their initial visit.

### **2.2 vHIT and saccades recording**

vHIT was conducted with a video-oculography device (ICS Impulse, GN Otometrics Inc., Denmark). The patient was asked to fixate on a visual target 1 meter in front of them in a sitting position. Approximately ten fast, unpredictable, small-amplitude, passive impulses were applied to each side by a skilled examiner. A separate examiner examined all impulses and deleted the ones containing blinking, lost track, poor calibration or low head velocity (less than  $150^\circ/\text{s}$  on lateral impulses). This process excluded 3 VM and 16 p-VM patients due to insufficient qualified samples (less than five impulses per side).

For saccadic data analysis, raw data were exported in XML format (eXtensible Markup Language). Saccades were retrieved using the open-source HitCal v5.3 software (<https://github.com/bendermh/HITCal>). Saccades in each impulse were numbered according to their sequences [16]. The analysis did not establish a time or velocity boundary for saccades. In order to avoid randomness, the rate of saccade occurrence was set to be greater than 50% for each subgroup. Otherwise, all saccades will be excluded from the analysis.

### **2.3 Data analysis**

The statistical analysis was conducted using the IBM SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). The unpaired student's t-test was used on parameters that were in accordance with normal distribution. In other cases, the Wann-Whitney test was applied. All

data were presented as mean  $\pm$  standard deviation. Non-dimensional parameters, such as absolute saccade velocity, were included in this study to eliminate possible influences caused by peak head velocity.

$$\text{Absolute saccade velocity} = (\text{saccade velocity})/(\text{peak head velocity})$$

Swarm, box and violin plots were combined to illustrate data distribution, statistical characteristics and sample vergence. In the violin plot, peaks showed more samples than valleys. Data visualization was generated using the Python 3.7 software (Python Software Foundation, DE, USA.).

### 3. Results

#### 3.1 General characters of VM patients

Clinical characteristics of the 14 VM patients are summarized in Table 1. Females outnumbered males by 11 to 3. The average age of these patients was  $44.21 \pm 11.93$  years. They all met the diagnostic criteria for VM [15] and experienced vestibular symptoms including spontaneous vertigo, vision-induced vertigo, positional vertigo, motion-induced vertigo and motion-induced dizziness. PN, HSN and SN were barely noticeable in these patients. Five patients had abnormal UW results.

**Table 1 Clinical features of VM patients**

Patient	Gender	Age (Year)	SN	PN	HSN	UW	Duration of Vestibular Syndrome Attacks	Course of Disease
#1	Female	52	/	/	/	L(18%)	Hours	3 years
#2	Female	43	/	/	/	L(63%)	Hours	2 years
#3	Female	38	/	/	/	L(51%)	Minutes	5 months
#4	Female	38	/	/	/	L(9%)	Days	10 years
#5	Female	58	/	/	/	L(42%)	Days	1 month
#6	Male	54	/	/	L(13)	L(42%)	Minutes	1 month
#7	Male	46	/	/	/	L(19%)	Hours	3 years
#8	Male	58	/	/	/	R(18%)	Hours	7 years
#9	Female	35	/	/	/	0	Days	2 years
#10	Female	38	/	/	/	R(5)	Hours	3 years
#11	Female	63	/	/	/	L(23%)	Hours	5 years
#12	Female	17	/	/	/	R(17%)	Hours	3 years
#13	Female	47	/	/	/	L(41%)	Hours	3 months
#14	Female	32	/	/	/	R(15%)	Hours	2 years

#### 3.2. Saccades in VM patients

Figure 1 shows saccades in all six semicircular canals (SCCs) on both sides. Randomly-occurring saccades (less than half of all impulses) were excluded from the analysis. Lateral SCC stimulation triggered most saccades, followed by the posterior SCC and anterior SCC. There was a high incidence of saccades for both lateral SCCs in these patients (86%, 12/14). Anterior and posterior SCC saccades appeared to occur randomly. On both sides, the second and third saccades were less frequently observed than the first saccade. Therefore, the first saccade from lateral SCC stimulation appeared to be the most crucial parameter among all saccade parameters to describe clinical features of VM.

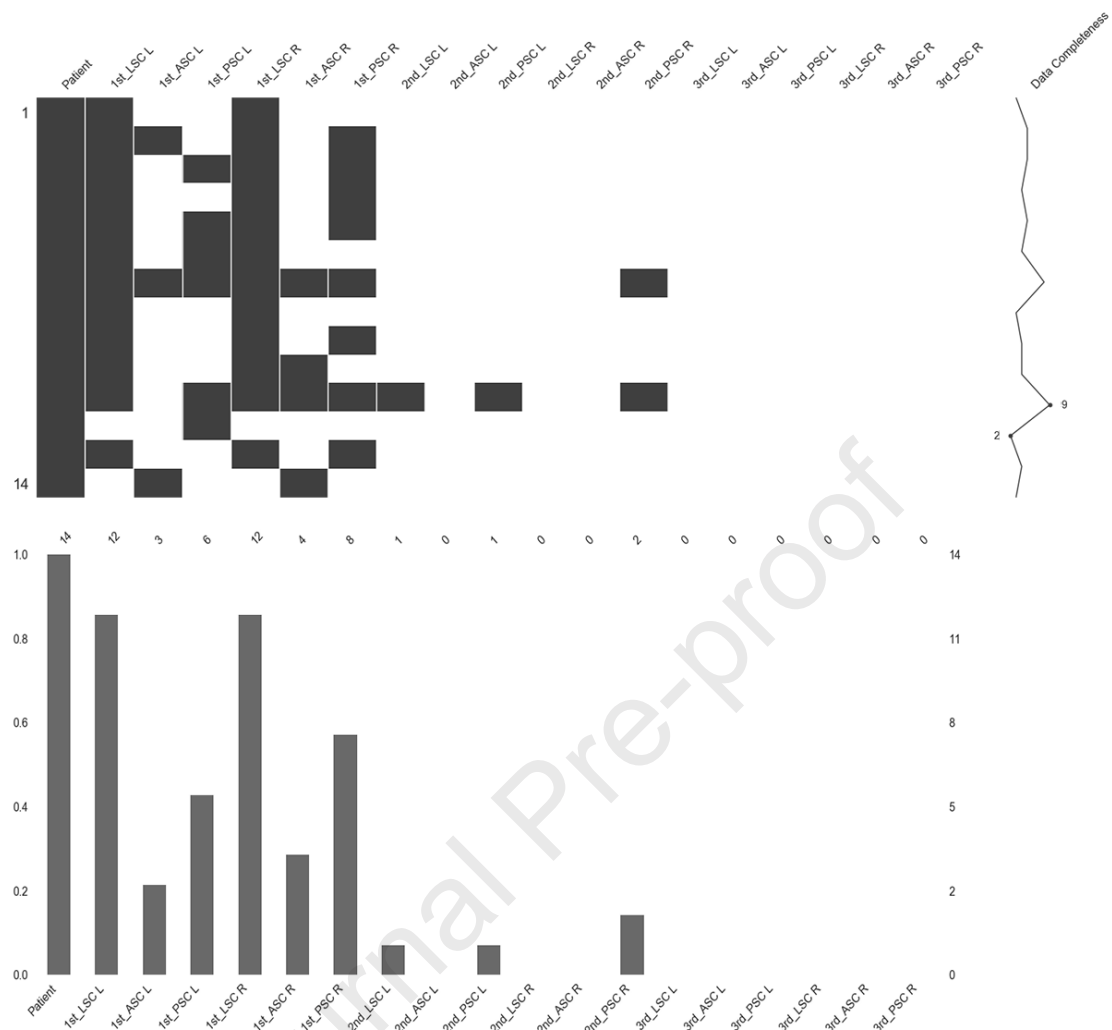


Figure 1. Completeness of saccades data for the six semicircular canals

ASC: anterior semicircular canal, PSC: posterior semicircular canal, LSC: lateral semicircular canal. 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> = the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> saccade.

Table 2 compares the first saccade on the left and right sides, showing identical interaural velocity and time characteristics. Coefficients of variation (CV) of velocity and time parameters showed no statistically significant differences, suggesting that saccades dispersity was equivalent on both sides. CV of latency indicated a relatively scattered pattern of distribution.

**Table 2. Comparison of 1<sup>st</sup> saccade parameters from LSC stimulation between the two sides in VM patients**

Parameters		L	R	P
Gain		0.92±0.07	0.97±0.08	0.066
Velocity	Velocity (°/s)	72.77±32.06	78.74±30.99	0.647
	CV of Velocity	0.37±0.13	0.30±0.11	0.185
	Abs. Velocity	0.34±0.14	0.37±0.13	0.659
	CV of Abs. Velocity	0.39±0.13	0.31±0.11	0.122
Time	Latency (ms)	288.90±61.74	279.65±70.01	0.735

CV of Latency                       $0.20 \pm 0.12$                        $0.21 \pm 0.07$                       0.796

CV: coefficient of variation (= standard deviation/mean); Abs. Velocity: absolute velocity (a non-dimensional parameter); LSC: lateral semicircular canal.

Figure 2 shows a detailed analysis of the first saccade in each VM patient. A: absolute velocities of small-amplitude saccades vary between 0.2 and 0.5 times the peak head velocity in most patients. B: latency of the first saccade from LSC stimulation varies from 200 ms (head movement ends at 140 ms) to 400 ms (recording ends at 560 ms).

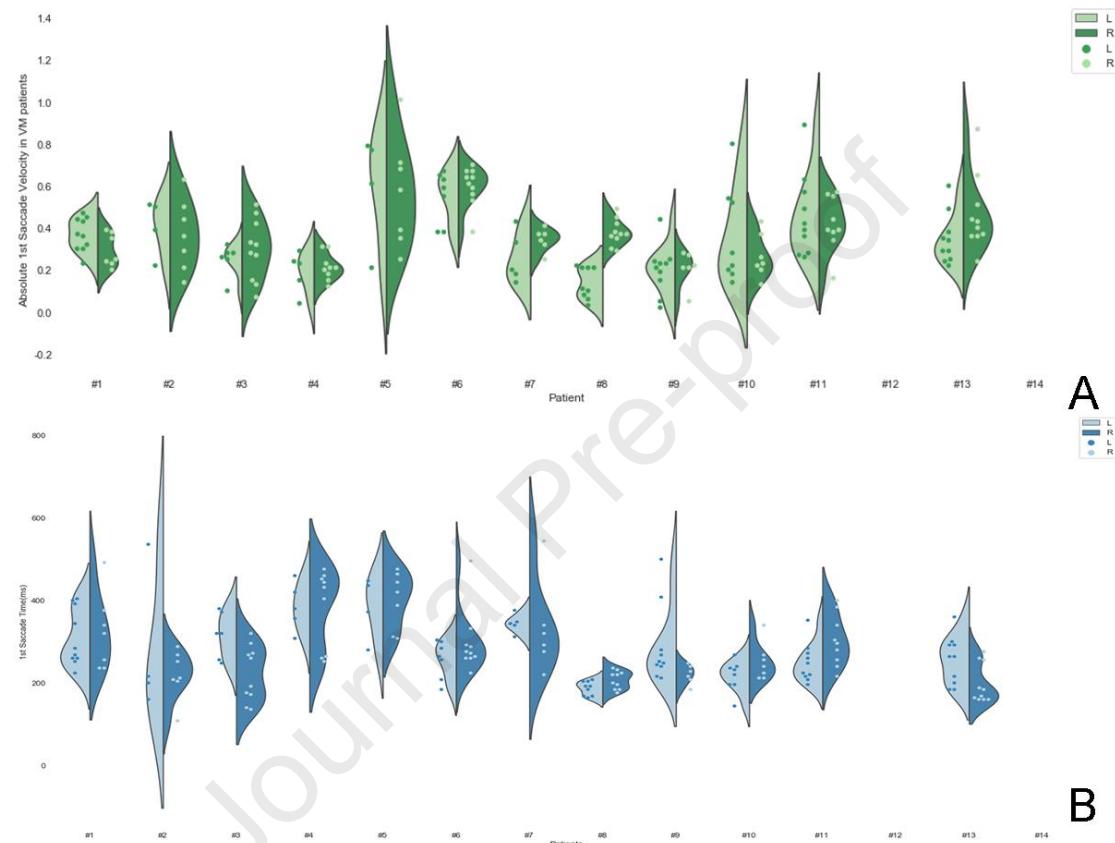


Figure 2. Analysis of the 1<sup>st</sup> saccade in individual VM patients. A: absolute velocity; B: saccade latency (ms).

### 3.3 Saccades in p-VM patients

No interaural differences in saccade characters were found among the 45 patients with p-VM (Table 3 and Figure 3). Both left and right sides presented small first saccades at approximately 1/3 of the peak head velocity (no more than half of the peak head velocity in general). The latency of the first saccade was 275 ms on left and 281 ms on right for lateral SCC stimulation with head movement ending at 140 ms. CV of latency indicated a scattered distribution pattern.

**Table 3, Comparison of 1<sup>st</sup> saccade parameters from lateral SCC stimulation between left and right sides in p-VM patients**

Parameters	L	R	P
------------	---	---	---



Gain		$0.96 \pm 0.08$	$0.98 \pm 0.09$	0.233
Velocity	Velocity( $^{\circ}$ /s)	$61.88 \pm 22.33$	$69.31 \pm 33.23$	0.279
	CV of Velocity	$0.29 \pm 0.10$	$0.31 \pm 0.12$	0.388
	Abs. Velocity	$0.31 \pm 0.12$	$0.34 \pm 0.14$	0.300
	CV of Abs. Velocity	$0.29 \pm 0.11$	$0.31 \pm 0.12$	0.401
Time	Latency (ms)	$275.08 \pm 68.12$	$280.83 \pm 73.55$	0.736
	CV of Latency	$0.25 \pm 0.10$	$0.22 \pm 0.12$	0.200

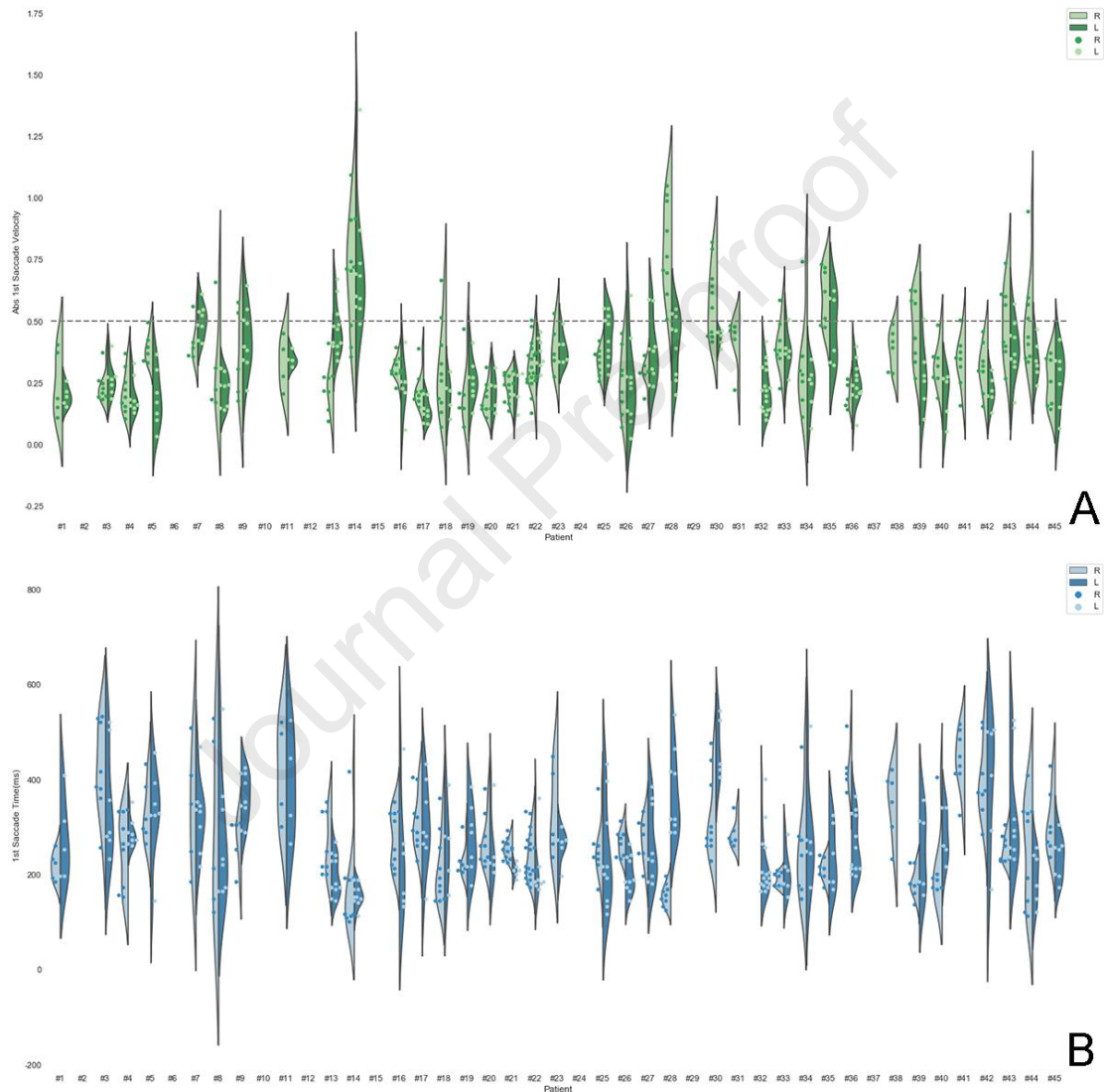


Figure 3. Analysis of 1<sup>st</sup> saccades in individual p-VM patients. A: absolute velocity; B: latency (ms).

### 3.4 Saccades in healthy controls

Among the 14 healthy controls (mean age =  $35.36 \pm 4.30$  years, females to males = 11:3), saccades were triggered in only four subjects, all unilateral and seemingly random. The saccade velocities varied from 0.1 to 0.5 times of the maximum head velocity. The interval between saccades ranged from 152 to 524 milliseconds.



#### 4. Discussion

Our findings show that saccades are commonly present in patients with VM and p-VM, usually bilateral from stimulation of lateral semicircular canals and in the presence of a normal VOR gain. In patients with VM, these saccades are small with a scattered distribution pattern (see Figure 4). In our study, parameters of saccades were essentially identical between the left and right sides. In healthy subjects, saccades in the presence of normal VOR gain were rare compared to VM patients and only on one side.

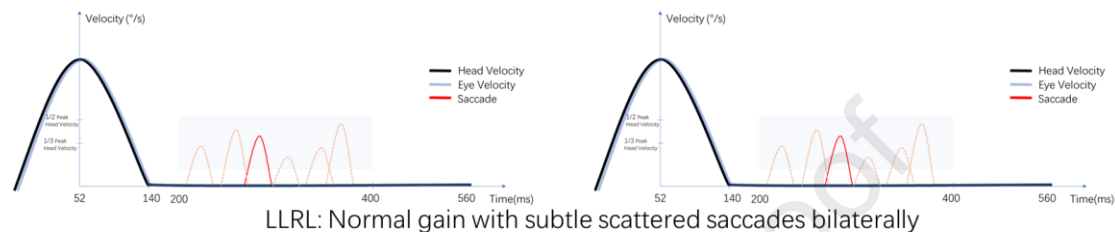


Figure 4. Saccades in VM patients (including p-VM). LLRL: left and right lateral SCCs

Preconceived notions suggest that subtle saccades without gain loss are always considered normal for peripheral and central vestibular systems. Such events have been ignored previously since vHIT gain is always the first concern. However, vHIT includes not only the VOR, but also saccades. VOR is an instant response to a passive head movement. By shifting the gaze, saccades can maintain the image in the fovea to minimize the visual-fovea gap. With vestibular deficits, saccade velocity and eye movement after VOR are related [17]. During VM attacks, there may be spontaneous nystagmus and persistent positional nystagmus [1, 2, 3], but they do not last long [12]. Saccades persist when symptoms subside, suggesting that potential dysfunction once existed.

The small amplitude of saccades in VM may suggest that vestibular function is relatively intact in the absence of symptoms. In addition to retinal slip, positional errors can also cause saccades [18]. This may partially explain why saccades are observed on the healthy side in vestibular neuritis and Meniere's disease (MD) [16, 19]. On the other hand, based on our findings, saccades appear to be randomly distributed on one side in healthy individuals, which is different from saccades in VM patients.

It is also possible that saccades may indicate some level of perception [20]. VM patients seem more likely to suffer from imbalance, motion sickness and anxiety [21]. In addition, patients with VM may experience abnormal spatial orientation integration [22, 23]. A recent study by Bonaldson suggests that patients with VM are likely to suffer from cognitive dysfunction [24]. Since there are no appropriate indicators of the patient's functional status, designing a rehabilitation program for VM patients is always challenging. Saccades may aid physicians in determining the disease status in patients with VM. Moreover, Saccades, as a sensitive parameter, may be an indicator of VM or p-VM syndrome and should be included in a screening vestibular test battery for evaluation of episodic vestibular disorders.

Further research regarding saccade changes in patients with VM should not be neglected. A proper vestibular function test is essential when it is challenging to differentiate VM from MD [10, 12]. Comparison of saccades between VM and MD patients may be helpful. Similar bilateral saccades may also indicate potential bilateral vestibular dysfunction, for which more thorough investigation is needed.

### Disclosure Statement

This research received no specific grant support. The authors declare that they have no conflicts of interest.

### Reference:

1. von Brevern M, Radtke A, Clarke AH, et al. Migrainous vertigo presenting as episodic positional vertigo. *Neurology*. 2004 Feb 10;62(3):469-72. doi: 10.1212/01.wnl.0000106949.55346.cd. PubMed PMID: 14872034.
2. Polensek SH, Tusa RJ. Nystagmus during attacks of vestibular migraine: an aid in diagnosis. *Audiol Neurotol*. 2010;15(4):241-6. doi: 10.1159/000255440. PubMed PMID: 19893305.
3. von Brevern M, Zeise D, Neuhauser H, et al. Acute migrainous vertigo: clinical and oculographic findings. *Brain*. 2005 Feb;128(Pt 2):365-74. doi: 10.1093/brain/awh351. PubMed PMID: 15601663.
4. Boldingh MI, Ljostad U, Mygland A, et al. Comparison of interictal vestibular function in vestibular migraine vs migraine without vertigo. *Headache*. 2013 Jul-Aug;53(7):1123-33. doi: 10.1111/head.12129. PubMed PMID: 23676003.
5. Jeong SH, Oh SY, Kim HJ, et al. Vestibular dysfunction in migraine: effects of associated vertigo and motion sickness. *J Neurol*. 2010 Jun;257(6):905-12. doi: 10.1007/s00415-009-5435-5. PubMed PMID: 20041331.
6. Huang TC, Wang SJ, Kheradmand A. Vestibular migraine: An update on current understanding and future directions. *Cephalalgia*. 2020 Jan;40(1):107-121. doi: 10.1177/0333102419869317. PubMed PMID: 31394919.
7. Lempert T, von Brevern M. Vestibular Migraine. *Neurol Clin*. 2019 Nov;37(4):695-706. doi: 10.1016/j.ncl.2019.06.003. PubMed PMID: 31563227.
8. Tweed D, Sievering D, Misslisch H, et al. Rotational kinematics of the human vestibuloocular reflex. I. Gain matrices. *J Neurophysiol*. 1994 Nov;72(5):2467-79. doi: 10.1152/jn.1994.72.5.2467. PubMed PMID: 7884472.
9. Kang WS, Lee SH, Yang CJ, et al. Vestibular Function Tests for Vestibular Migraine: Clinical Implication of Video Head Impulse and Caloric Tests. *Front Neurol*. 2016;7:166. doi: 10.3389/fneur.2016.00166. PubMed PMID: 27746761; PubMed Central PMCID: PMC444462.
10. Blodow A, Heinze M, Bloching MB, et al. Caloric stimulation and video-head impulse testing in Meniere's disease and vestibular migraine. *Acta Otolaryngol*. 2014 Dec;134(12):1239-44. doi: 10.3109/00016489.2014.939300. PubMed PMID: 25399882.
11. Weber KP, Aw ST, Todd MJ, et al. Head impulse test in unilateral vestibular loss: vestibulo-ocular reflex and catch-up saccades. *Neurology*. 2008 Feb 5;70(6):454-63. doi: 10.1212/01.wnl.0000299117.48935.2e. PubMed PMID: 18250290.

12. Calic Z, Nham B, Taylor RL, et al. Vestibular migraine presenting with acute peripheral vestibulopathy: Clinical, oculographic and vestibular test profiles. *Cephalalgia*. 2020;3(2):251581632095817.
13. Rey-Martinez J, Batuecas-Caletrio A, Matino E, et al. HITCal: a software tool for analysis of video head impulse test responses. *Acta Otolaryngol*. 2015 Sep;135(9):886-94. doi: 10.3109/00016489.2015.1035401. PubMed PMID: 25857220.
14. Matíño-Soler E, Rey-Martinez J, Trinidad-Ruiz G, et al. A new method to improve the imbalance in chronic unilateral vestibular loss: the organization of refixation saccades. *Acta Otolaryngol*. 2016;136(9):894-900. doi: 10.3109/00016489.2016.1172730. PubMed PMID: 27109262.
15. Lempert T, Olesen J, Furman J, et al. Vestibular migraine: diagnostic criteria. *J Vestib Res*. 2012;22(4):167-72. doi: 10.3233/VES-2012-0453. PubMed PMID: 23142830.
16. Du Y, Liu X, Ren L, et al. Exploratory saccades data analysis of video head impulse test in different Meniere's disease stages. *J Vestib Res*. 2022;32(2):183-192. doi: 10.3233/VES-201642. PMID: 34366304.
17. John LR, Zee DS. *The neurology of eye movements*. 2015.
18. de Brouwer S, Yuksel D, Blohm G, et al. What triggers catch-up saccades during visual tracking? *J Neurophysiol*. 2002 Mar;87(3):1646-50. doi: 10.1152/jn.00432.2001. PubMed PMID: 11877535.
19. Du Y, Ren L, Liu X, et al. The characteristics of vHIT Gain and PR score in peripheral vestibular disorders. *Acta Otolaryngol*. 2021 Jan;141(1):43-49. doi: 10.1080/00016489.2020.1812715. PubMed PMID: 32930021.
20. Grüsser OJ. *Vision and Eye Movements*. Springer Berlin Heidelberg; 1983.
21. Balci B, Akdal G. Imbalance, motion sensitivity, anxiety and handicap in vestibular migraine and migraine only patients. *Auris Nasus Larynx*. 2020 Oct;47(5):747-751. doi: 10.1016/j.anl.2020.02.015. PubMed PMID: 32178946.
22. Winnick A, Sadeghpour S, Otero-Millan J, et al. Errors of Upright Perception in Patients With Vestibular Migraine. *Front Neurol*. 2018;9:892. doi: 10.3389/fneur.2018.00892. PubMed PMID: 30425678; PubMed Central PMCID: PMC6218433.
23. King S, Priesol AJ, Davidi SE, et al. Self-motion perception is sensitized in vestibular migraine: pathophysiologic and clinical implications. *Sci Rep*. 2019 Oct 4;9(1):14323. doi: 10.1038/s41598-019-50803-y. PubMed PMID: 31586151; PubMed Central PMCID: PMC6778132.
24. Donaldson LB, Yan F, Liu YF, et al. Does cognitive dysfunction correlate with dizziness severity in patients with vestibular migraine? *Am J Otolaryngol*. 2021 Nov-Dec;42(6):103124. doi: 10.1016/j.amjoto.2021.103124. PubMed PMID: 34166962.