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Saccades of video head impulse test in Meniere's disease and Vestibular Migraine: What can we learn from?

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ABSTRACT

Background: Saccades are often observed on video head impulse tests (vHIT) in patients with Meniere's Disease (MD) and Vestibular Migraine (VM). However, their saccadic features are not fully described.
Objective: This study aims to identify the saccades characteristics of MD and VM.
Methods: 75 VM patients and 103 definite unilateral MD patients were enrolled in this study. First raw saccades were exported and analyzed. The VM patients were divided into left and right based on their ears, while the MD patients were separated into affected and unaffected subgroups based on their audiograms and symptoms.
Results: The MD patients have more saccades on the affected side (85% vs. 69%), and saccade velocity is more consistent than the contralateral side (shown by the coefficient of variation). The saccades occurrence rates on both sides are similar in VM (77% vs. 76%), as are other saccadic parameters. The MD patients have more significant inter-aural differences than the VM patients, manifested in higher velocity (p-value 0.000), earlier arriving (p-value 0.010), and more time-domain gathered (p-value 0.003) on the affected side.
Conclusions: Bilateral saccades are commonly observed in MD and VM. In contrast to MD, saccades on VM are subtle, scattered, and late-arrived. Furthermore, the MD patients showed inconsistent saccadic distribution with more velocity-uniform saccades on the affected side.

1. Introduction

Meniere's Disease (MD) and Vestibular Migraine (VM) are two common episodic vestibular syndromes (EVS). In some cases, it is difficult to distinguish between them because they may share similar symptoms (Blödow et al., 2014; Radtke et al., 2002, 2012). Although auditory signs are not required for diagnosing VM, up to 38% of the patients may exhibit this symptom (Neff et al., 2012). During the attack, MD patients may have migraine symptoms such as headache, phonophobia, and photophobia (Blödow et al., 2014).

The vestibular function findings may associated with clinical symptoms. VM patients usually have normal vestibular examination results when symptom-free (Huang et al., 2020; Lempert and von Brevern, 2019). Spontaneous nystagmus and persistent positional nystagmus are frequently shown in the acute stage (Polensek and Tusa, 2010; von Brevern, 2004; von Brevern et al., 2004), and head-shaking nystagmus may occur during the interictal period (Boldingh et al., 2013; Jeong et al., 2010). Regarding the MD, it has been reported that caloric asymmetry increases with the disease progression (Kharkheli et al., 2019). Besides, a correlation exists between saccade velocity and disease severity (Du et al., 2022b).

Many researchers have discussed the vHIT sensitivity to VM and MD, but a definitive conclusion has yet to be reached. The reason could be that the two vHIT parameters-vestibular ocular reflex (VOR) gain and catch-up saccades – are inconsistent. The low VOR gain is observed in 9–11% of VM patients, making the researchers

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conclude that vHIT is less sensitive than the caloric test (Blödow et al., 2014; Kang et al., 2016). Compared to the low sensitivity of VOR gain, saccades are frequently shown in VM (Calic et al., 2020; Huang et al., 2020). A follow-up study confirmed that VOR gain and saccades were associated with MD progress (Yacovino et al., 2017). Hannigan et al. proposed a high caloric asymmetry and a normal VOR gain as helpful markers for identifying MD (Hannigan et al., 2021). However, it is noted that saccades are not as uncommon as expected among MD patients (55%) (Blödow et al., 2013).

The vague understanding of vHIT leads to its limited clinical application. It is evident that recurrent saccades occur in MD and VM, but in vHIT reports, they are routinely ignored out of concern that no significant loss of gain is observed. In the traditional sense, Saccade is less measurable and definable than VOR gain (Weber et al., 2008). PR score is one of the few quantitative saccadic parameters which could indicate vestibular recovery (Matiñó-Soler et al., 2016; Rey-Martinez et al., 2015). However, all unapparent saccades (the software sets the saccade velocity higher than 65°/s) were eliminated from the PR score, affecting the detection rate of subtle saccades in MD and VM patients. Although it is understood that Saccade has a role in diagnosis, the relationship between the saccades and the two common EVS needs in-depth study. Besides, our former research has supported the importance of Saccades for EVS identification (Du et al., 2022). Therefore, the present study aims to identify the characteristics of saccades in MD and VM.

2. Materials and methods

2.1. Subjects

A retrospective review of patients admitted to the vertigo clinic of the Chinese PLA General Hospital between July 2020 and November 2021 was conducted. After ruling out 26 patients lacking enough data samples or poor vHIT results, 75 patients met the VM diagnostic criteria (Lempert et al., 2012), and 103 met the definite MD diagnosis criteria(Lopez-Escamez et al., 2015) were enrolled. MD patients with migraine symptoms and bilateral MD were not included in this study. Due to the comparison between VM patients and normal subjects has been discussed in our former work(Du et al., 2022a), no healthy controls were matched for this study. The Chinese PLA General Hospital waived ethical approval, and all procedures were routine tests.

2.2. vHIT and saccades recording

A video-oculography device (ICS Impulse, GN Otometrics Inc., Denmark) was used for the vHIT procedure. Patients were instructed to gaze at a visual target 1 m away. Approximately ten small-amplitude, fast, unpredictable impulses were sent in each direction. A skilled experimenter made the recordings. Another reviewed all the impulses and deleted those with blinking eyes, losing track, poor calibration, or low peak velocity (less than 150°/s).

In order to obtain an exploratory analysis, the raw data were exported in XML (eXtensible Markup Language) format. An open-source HitCal v5.3 was used for extracting saccades, which were then read by MATLAB (R2021a, MathWorks, Natick, MA) through the HITCal package. The first saccade on the lateral semicircular canal is a more reliable and effective parameter (Du et al., 2022; Du et al., 2022b). Therefore, in this study, only the first saccade was investigated. In order to capture the subtle saccades shown in the report, no velocity or time boundaries were defined. To avoid randomness, the number of saccades should be at least half. Otherwise, saccades would be deleted. As the MD patients have audiograms showing the affected side, saccades were divided into affected and unaffected. In VM patients, saccades were subdivided by the left and the right ear.

2.3. Exploratory saccades analysis and statistical analysis

To illustrate data completeness, statistical characteristics, and pair-wise comparisons, a missing value chart, bar chart, and slope chart were used. Data visualization was generated with Python (Python Software Foundation, DE, USA.) 3.7 program.

The numerical variables were presented as mean ± standard deviation (SD). A Chi-square test was used to compare categorical variables presented as counts or percentages. We used the unpaired student t-test when the parameters followed a normal distribution. In other cases, the Wann-Whitney test was used. In order to examine pair-wise differences when saccades occurred bilaterally, a paired *t*-test was added. Statistical significance was defined as a p-value of 0.05. All analyses were performed using IBM SPSS 20.0 (SPSS Inc., Chicago, IL, USA). This study also considers non-dimensional parameters, Cov (Coefficient of Variation), on both time and velocity.

$$\text{Coefficient of variation (CoV)} = (\text{standard deviation} \ / \ \text{mean}) = (\text{SD} \ / \ \overline{X})$$

3. Results

3.1. General characters of MD and VM patients

In this study, 103 MD patients and 75 VM patients were enrolled (Table 1). There are more females than males (56:47) in MD. Their average age is 51.11 ± 12.34, and their left-to-right ratio is 49: 54. According to MD stages based on a four-tone average of 0.5, 1, 2, and 3 kHz (Committee on Hearing and Equilibrium, 1995): stage 1 ($\leq$25 dB, N = 10), stage 2 (26–40 dB, N = 23), stage 3 (41–70 dB, N = 51) and stage 4(> 70 dB, N = 19).

3.2. Exploratory saccade analysis for MD and VM patients

Fig. 1 illustrates the occurrence of saccades in the lateral semicircular canals in each patient. In general, saccades are bilaterally appearing on most VM and MD patients. However, to be specific, MD patients trigger more saccades on the affected side (88/103) than on the contralateral side (71/103, $p = 0.011$, Table 2). Additionally, the cov of saccade velocity on the unaffected side is significantly higher ($p = 0.007$, as shown in Table 2), implying that the saccade velocities are more scattered. The presence of saccades in VM patients has a synchronized appearance (58:57), as seen in Fig. 1 and Table 3. The parameters for saccades are bilaterally equivalent ($p > 0.05$).

3.3. Pair-wise comparison for bilateral saccades

The saccades found in 3.2 bilaterally appeared on both diseases. Therefore, a further pair-wise comparison is needed. 66 out of 103 MD patients have bilateral saccades. Cov of Saccade Velocity shows a lower value on the affected side ($p = 0.004$, as shown in Fig. 2). The red lines indicate that most MD patients have a lower cov of Saccade Velocity (gathered) on the affected side. As for VM, 52 of 75 patients exhibit bilateral saccades, and none of these features is statistically different.

Table 1
General clinical characters for MD and VM patients.

Clinical characters		Values
MD	N	103
	Female: Male	56:47
	Age	51.11 ± 12.34
	Affected Side (Left: Right)	49:54
	MD Stages (I: II: III: IV)	10: 23: 51: 19
VM	N	75
	Female: Male	49:26
	Age	47.24 ± 13.88

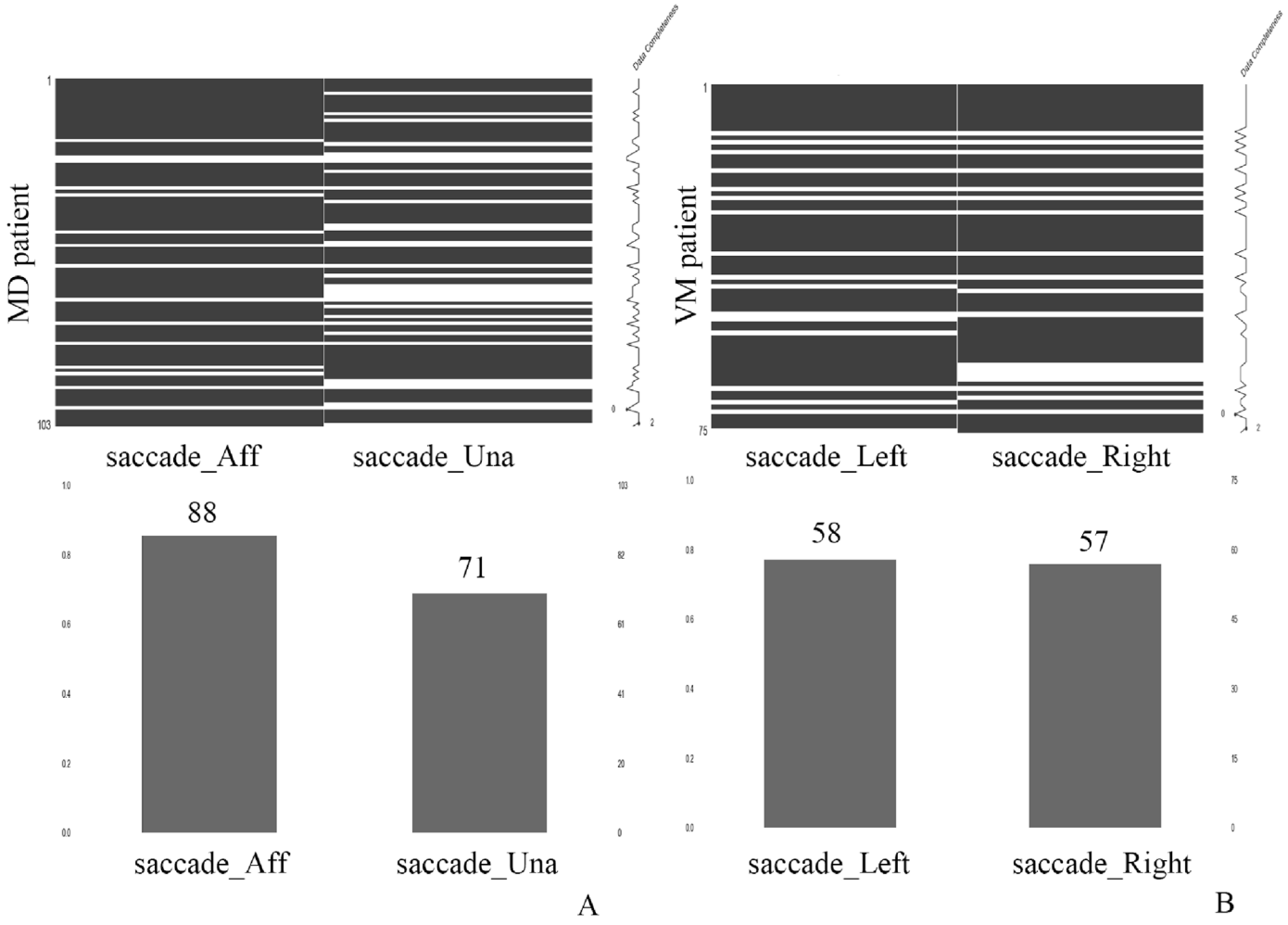

Fig. 1. Saccade occurrences for each MD (A) and VM patient (B). Abbreviations of Aff and Una are for the affected and unaffected sides in unilateral MD patients.

Table 2
Comparison of saccades on both sides on MD patients.

Parameters	Affected	Unaffected	*P*
Saccade Incidence	**88/103 (85%)**	**71/103 (69%)**	**0.011***
Saccade Velocity	95.74 ± 51.06	88.57 ± 44.07	0.347
Saccade Time	95.90 ± 18.90	98.31 ± 20.24	0.437
Cov of Saccade Velocity	**0.26 ± 0.11**	**0.32 ± 0.14**	**0.007****
Cov of Saccade Time	0.12 ± 0.07	0.14 ± 0.07	0.076

Table 3
Comparison of saccades on both sides on VM patients.

Parameters	Left	Right	*p*
Saccade Incidence	58/75 (77%)	57/75 (76%)	0.847
Saccade Velocity	67.12 ± 26.13	72.70 ± 31.06	0.299
Saccade Time	105.62 ± 16.39	106.31 ± 16.32	0.823
Cov of Saccade Velocity	0.31 ± 0.12	0.29 ± 0.11	0.428
Cov of Saccade Time	0.16 ± 0.07	0.16 ± 0.06	0.763

3.4. The difference in bilateral saccades in MD and VM patients

The comparison between both ears shows many similarities (Fig. 2). However, Table 4 displays the interaural saccadic differences between MD and VM patients. The following interaural features were assessed: the absolute differences between the left and right sides in patients with VM and the absolute differences between the affected and unaffected sides in patients with MD. The

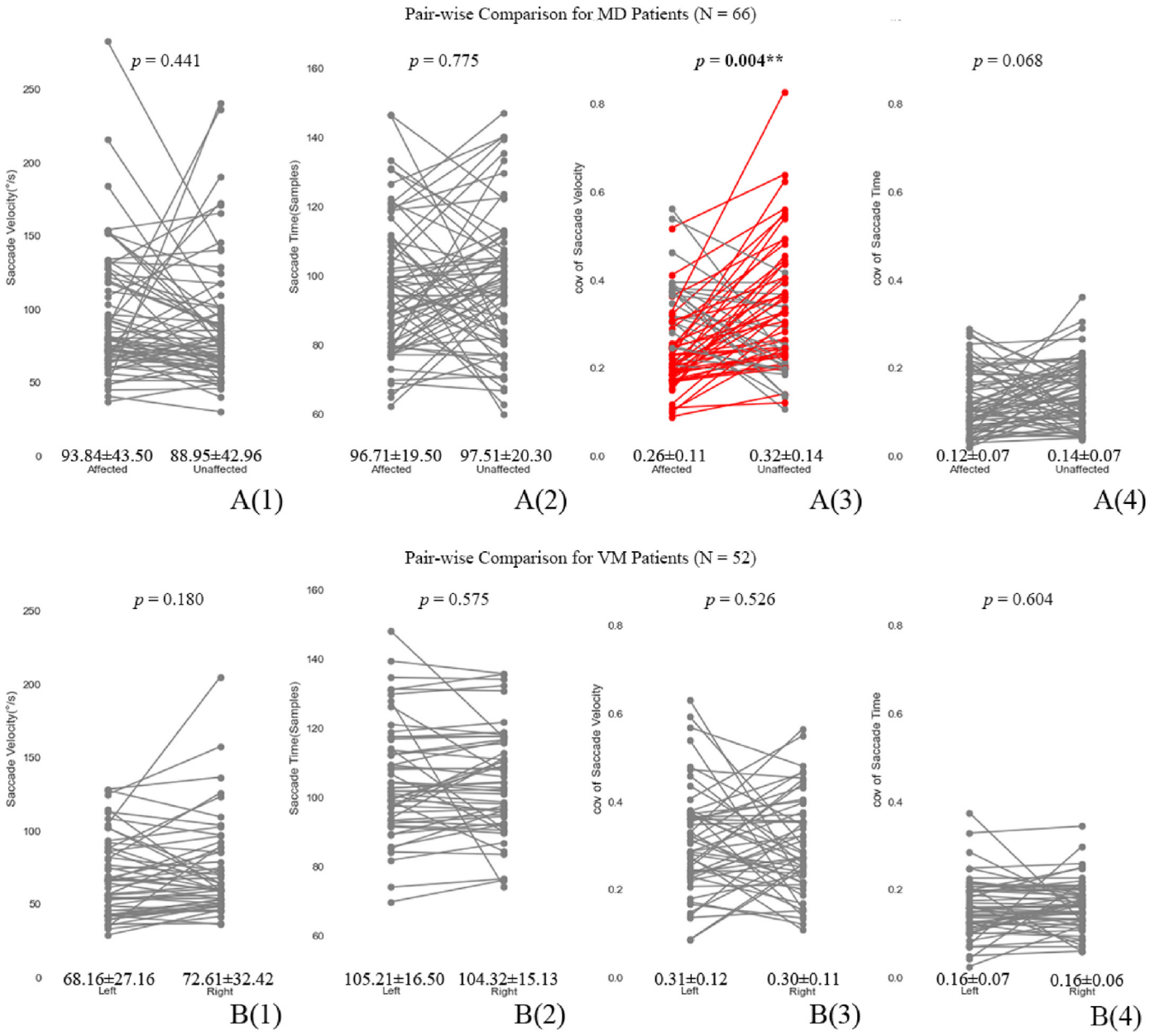

Fig. 2. Pair-wise Saccade Features Comparisons of MD (A(1) - A(4)) and VM Patients (B(1)−B(4)). A red line connects the bilateral saccades of the MD-affected side with a lower cov of saccade velocity.

Table 4
Inter-aural comparison for MD and VM patients.

Inter-Aural Parameters		MD	VM	*p*
Difference	**Saccade Velocity**	**32.32 ± 39.89**	**15.86 ± 17.92**	**0.004****
	Saccade Time	**17.88 ± 13.68**	**6.49 ± 9.37**	**0.000*****
	Cov of Saccade Velocity	0.13 ± 0.11	0.11 ± 0.09	0.147
	Cov of Saccade Time	**0.07 ± 0.06**	**0.04 ± 0.06**	**0.005****
Mean	**Saccade Velocity**	**91.39 ± 34.81**	**70.39 ± 27.48**	**0.000*****
	Saccade Time	**97.11 ± 16.38**	**104.76 ± 14.77**	**0.010***
	Cov of Saccade Velocity	0.29 ± 0.10	0.30 ± 0.09	0.452
	Cov of Saccade Time	**0.13 ± 0.06**	**0.16 ± 0.05**	**0.003****

mean values were also calculated. In this comparison, three of the four parameters are statistically significant in differences of Saccade Velocity (p-value 0.004), Saccade Time (p-value 0.000), and cov of Saccade Time (p-value 0.005), as well as the means of Saccade Velocity (p-value 0.000), Saccade Time (p-value 0.010), and cov of Saccade Time (p-value 0.003).

Patients with MD have higher velocities, earlier arrival times, and more gathered saccades than patients with VM, particularly on the affected side. Conversely, bilateral saccades in VM patients are small-amplitude, late-arrived, and scattered.

4. Discussion

Although some studies have reported the sensitivity of VOR gain on MD and VM, the knowledge about saccades needs to be improved. This exploratory analysis shows that saccades are typical in MD and VM, particularly in the horizontal semicircular canals. In MD, saccade asymmetry in incidence and velocity could be observed, whereas saccades are equally distributed (small amplitude and scattered) in VM patients. Compared to the VM, MD can be identified by the early arrival, high velocity, and more velocity-consistent of saccades on the affected ear.

Many physicians have stressed the importance of vestibular function examinations in detecting EVS. Yilmaz et al. reported a higher likelihood of abnormal caloric results and VOR loss in MD than in VM (Yilmaz et al., 2021). The findings in this study suggest that when considering saccades, vHIT is more sensitive to both diseases than once thought. As previously discussed, saccade velocity increases with MD progress (Du et al., 2022b). An easily overlooked aspect is that vHIT contains not only angular VOR but also saccade. As with the VOR gain, the saccades velocity indicates the vestibular impairment (Leigh and Zee, 2015). Furthermore, saccades on the healthy side of vestibular neuritis and MD may be due to position errors, an intuitive process (de Brouwer et al., 2002; Du et al., 2021, 2022b). The combined input of oculomotor and cervical proprioception is another saccadic trigger factor (MacDougall and Curthoys, 2012; Van Nechel et al., 2018).

The saccade mechanism in VM needs to be re-recognized. Peripheral vestibular dysfunction is common in these patients (Baloh, 1997), who may experience kinephobia, imbalance, motion sickness, anxiety, and abnormal sensory integration for spatial orientation (Balcı and Akdal, 2020; Cutrer and Baloh, 1992; King et al., 2019; Neuhauser et al., 2001; Winnick et al., 2018). Spontaneous nystagmus and persistent positional nystagmus may be evident in acute attacks (Cutrer and Baloh, 1992; Neuhauser and Lempert, 2004; Polensek and Tusa, 2010; von Brevern, 2004; von Brevern et al., 2004), but those symptoms usually do not last long(Calic et al., 2020). As a result of the spontaneous nystagmus, VOR gain loss and apparent saccades may be observed. Saccades may not disappear as soon as symptoms subside. Recognizing saccades makes it possible to find evidence of vestibular dysfunction. In addition, the role of saccades in vestibular function, stability of gaze, and balance performance have been found(Anson et al., 2016; Batuecas-Caletrio et al., 2020; Korsager et al., 2017; Xie et al., 2017).

Although the caloric test has been reported to have higher sensitivity in MD patients (42%–76%)(Neff et al., 2012; Park et al., 2005; Perez and Rama-Lopez, 2003; Shin et al., 2013; Wang et al., 2012) than in VM patients (7%–25%)(Boldingh et al., 2013; Neff et al., 2012; Neugebauer et al., 2013; Shin et al., 2013), its ineffectiveness and discomfort may allow limited clinical use. On the other hand, this study reveals that saccade is a sensitive parameter (77% and 85% for VM and MD, respectively). The phenotypes of saccades may serve as reference tools for EVS diagnosis. In light of this, we should update our knowledge about saccades and pay more attention to them when performing clinical examinations. As different symptoms require different treatment strategies, future studies should examine the effects of migraines on saccadic responses.

5. Conclusion

Bilateral saccades without gain loss are frequently shown in MD and VM. This study identified two saccadic phenotypes of both diseases. VM saccades are more subtle and scattered and arrived later than MD saccades. MD patients, however, had a greater degree of interaural differences, with more velocity-consistent saccades on the side of the affected ear.

Declaration of competing interest

None of the authors have potential conflicts of interest to be disclosed.

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