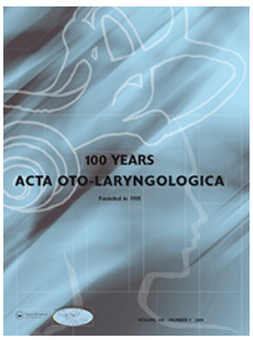

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RESEARCH ARTICLE

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Persistent static imbalance among acute unilateral vestibulopathy patients could be related to a damaged velocity storage system

Min Tae Kim, Jung Hyun Ahn, Sang Hyub Kim, Ji Eun Choi, Jae Yun Jung and Min Young Lee

Department of Otolaryngology-Head & Neck surgery, Dankook University, College of Medicine, Cheonan, Republic of Korea

ABSTRACT

Background: Acute unilateral vestibulopathy (AUV) is common but, the course of disease recovery is variable. Moreover, the final recovery status might vary between subjects. The remaining symptoms of these patients indicate the poor recovery of static imbalance, which could limit social activities and decrease their quality of life.

Objective: To determine the possible predictive parameters of prolonged static imbalance (PSI) among acute AUV, we compared several vestibular function test (VFT) results between control vestibulopathy (CV) and PSI patients.

Materials and methods: Subjects were divided into two groups: PSI and CV. PSI was determined by the observation of spontaneous nystagmus at 1 month after discharge from the hospital. VFT results taken during the initial symptoms were compared.

Results: Increased phase lead was observed in low-frequency stimulations ($p < .05$), while the other test results failed to reveal a significant difference. These results indicate that a larger phase lead, which is related to a decrease in the time constant, could be responsible for the delayed recovery of static imbalance.

Conclusion and significance: The phase lead was higher in the PSI group compared to the CV group, suggesting the possible role of phase as a parameter to predict the delayed compensation of static imbalance.

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KEYWORDS
Static imbalance; acute unilateral vestibulopathy; rotatory chair test; phase lead

Introduction

Acute unilateral vestibulopathy (AUV) is one of the common diagnoses made in the otologic clinic. It was the third most common peripheral vestibular disorder in a large cohort (>22,000 patients) at a vertigo clinic [1]. Its annual incidence has been reported to be 3.5 and 15.5 per 100,000 persons [2,3]. The etiology of this condition remains unclear but many animal and human studies have supported the viral infection theory [2–5]. It is presumed that a virus such as the herpes simplex virus resides in the vestibular ganglion and that certain factors are able to provoke the replication of this virus, resulting in inflammation and edema leading to the degeneration of neurons of the vestibular ganglion cells [6].

AUV is diagnosed initially by the symptomatic history of the patient and by clinical examination, with additional laboratory examination if available. The key symptoms of AUV are a single episode of spinning vertigo, external vertigo (not self-spinning), gait and posture imbalance toward the lesion side, and symptoms of nausea [6]. The most important clinical sign and physical finding is horizontal-torsional spontaneous nystagmus (SN) beating toward the unaffected ear with a varying degree of the vertical component. Laboratory examinations, including the so-called vestibular function test (VFT), utilize a variety of equipment to evaluate static imbalance, as well as the status of the vestibular ocular and vestibulo-colic reflex. Static imbalance, which is caused by a decreased resting firing rate of the affected vestibular peripheral afferents [7], can be evaluated by the observation and measurement of SN by eye monitoring (e.g. videonystagmography [VNG]), as well as by specialized tests such as the subjective visual vertical test [8].

After the acute stage, most of the symptoms of AUV progressively improve via a process called vestibular compensation; this process is facilitated by therapeutic exercises [6]. Vestibular compensation is composed of two distinct phases. First, static compensation, which improves the reduced firing rate of the affected vestibular neuron by complicated central processes, takes place followed by dynamic compensation using adaptation, substitution, and habituation [7]. Compensation of static imbalance happens relatively early on, compared to dynamic compensation [9]. The disappearance of SN several days or weeks after the onset of dizziness supports this theory. However, the course of disease recovery in AUV is extremely variable and shows high inter-subject variation. Moreover, the final recovery status might vary between subjects [7]. It is common to encounter AUV patients who complain of subjective disequilibrium and still show SN a month after onset. The remaining symptoms

CONTACT Min Young Lee eyeglass210@gmail.com Department of Otolaryngology-Head & Neck surgery, College of Medicine, Dankook University, Cheonan, Chungnam-do 330-714, Korea

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and SN of these patients indicate the poor recovery of static imbalance, which could limit social activities and decrease their quality of life. Thus, we separated AUV patients into two groups according to the presence of SN, which represents the presence of static imbalance at 1 month after hospital stay, and compared the initial VFT outcomes, to investigate those outcomes that are associated with delayed static imbalance.

Materials and methods

Subjects and design

We retrospectively reviewed the relevant patient data from January 2014 to July 2017. This study was approved by the Institutional Review Board of Dankook University Hospital. Initially, all patients who were admitted due to a severe single episode of spinning-type dizziness were enrolled. Among them, patients who were diagnosed with Meniere's disease, benign paroxysmal positional vertigo, migraine-associated vertigo, and central vertigo during follow-up were excluded. All patients were treated with Ginkgo biloba extract (EGb761) i.v. for 5 days and per oral for the following days. During the admission, vestibular rehabilitation exercise was educated. Sedatives including diazepam and dimenhydrinate usage were limited (used only in severe symptomatic cases, has not been used in regularly scheduled bases). At the initial VFT, all patients were diagnosed as acute unilateral vestibulopathy by the caloric test, rotatory chair test (RCT), or video head impulse test (vHIT). Sedative drugs are restricted before (at least within 24 hours prior to test) VFT thoroughly. Among them, patients who showed spontaneous nystagmus (2 degrees/sec with none-visual fixation) at 1 month after discharge were classified as the persistent static imbalance (PSI) group, and those who did not were classified as the control vestibulopathy (CV) group. Demographic data and VFT results were compared between the groups.

Vestibular function test

Among the various VFTs, the degree of initial nystagmus on VNG (Micromedical, Chatham, IL), percentage of canal paralysis (CP) in the bithermal caloric test (using 30 °C [cool] and 44 °C [warm] water), averaged parameters of the RCT (Micromedical, Chatham, IL), and gain value of the vHIT (ICS Impulse, Otometrics, Denmark) were analyzed. In VNG, the amplitude of nystagmus in degrees at the resting status (SN) and amplitude of nystagmus after head shaking (2 Hz, 10–20 sec) were included. In the caloric test, patients who had a CP of more than 25% were regarded as abnormal. The average values of the gain, phase, and asymmetry at three frequencies (0.04, 0.16, and 0.64 Hz) were compared in a slow harmonic acceleration (SHA) analysis of RCT. As for the gain value of vHIT, the bilateral gain values of three semicircular canals (anterior, horizontal, and posterior) were analyzed. For the vertical canal, a gain value lower than 0.6 was regarded as abnormal. For the horizontal canal, a gain value lower than 0.8 was regarded as abnormal.

Statistical analysis

All data were analyzed by the GraphPad Prism (GraphPad Software, La Jolla, CA) or SPSS (IBM Corp., Armonk, NY) software. A Kolmogorov–Smirnov test was used to determine whether the data were parametric or non-parametric. Significant differences between the CV and PSI group were statistically analyzed using a *t*-test in the case of a parametric distribution and Mann–Whitney *U*-test in the case of a non-parametric distribution, while Fisher's exact test was used for the cross-tabulation analysis. A *p*-value less than .05 was considered to indicate statistical significance and was defined as $^{*}p < .05$, $^{**}p < .01$, and $^{***}p < .001$, respectively.

Results

Demographic data

The mean age of the PSI group ($n = 17$) was 58.8 ± 8.25 years and that of the CV group ($n = 30$) was 54.6 ± 11.1 years; there was no significant difference between the two groups (independent *t*-test: $t = 1.363$, df = 45, $p = .18$). Both groups showed a male predominance (PSI: 64.3%; CV: 73.3%). The length of hospital stay was 6.2 ± 2.5 days in the PSI group and 4.5 ± 2.2 days in the CV group. The hospital stay was significantly longer in the PSI group (independent *t*-test: $t = 2.315$, df = 45, $p = .03$). The time interval between onset and the initial test was about 1 day in both groups, without significance (Man–Whitney test: $U = 238$, $p = .69$) (Table 1).

Vestibular function test

The initial SN of the PSI group was 9.9 ± 7.6 degrees and that of the CV group was 5.1 ± 4.1 degrees. SN was greater in the PSI group, but without significance (Man–Whitney test: $U = 176$, $p = .08$) (Figure 1(A)). Head shaking nystagmus (HSN) at the initial time point was 8.6 ± 3.6 and 5.5 ± 3.5 degrees in the PSI and CV group, respectively, and did not show a significant difference (independent *t*-test: $t = 1.827$, df = 39, $p = .08$) (Figure 1(B)). Two patients in the CV group and four patients in the PSI group who had a large SN were unable to open their eyes after head shaking and were excluded from the analysis.

In terms of the bithermal caloric test, there was no significant difference of averaged canal paresis value between PSI group and CV group (independent *t*-test: $t = -0.344$, df

Table 1. Demographic data of persistent static imbalance (PSI) group and control vestibulopathy (CV) group.

	PSI group ($n = 17$)	CV group ($n = 30$)
Mean age	58.8 (±8.25)	54.6 (±11.1)
Male (%)	11 (64.7)	22 (73.3)
Female (%)	6 (35.3)	8 (26.7)
Admission day (day)	6.2 (±2.5)	4.5 (±2.2)
Interval of onset to test (day)	1.0 (±1.1)	1.0 (±0.8)

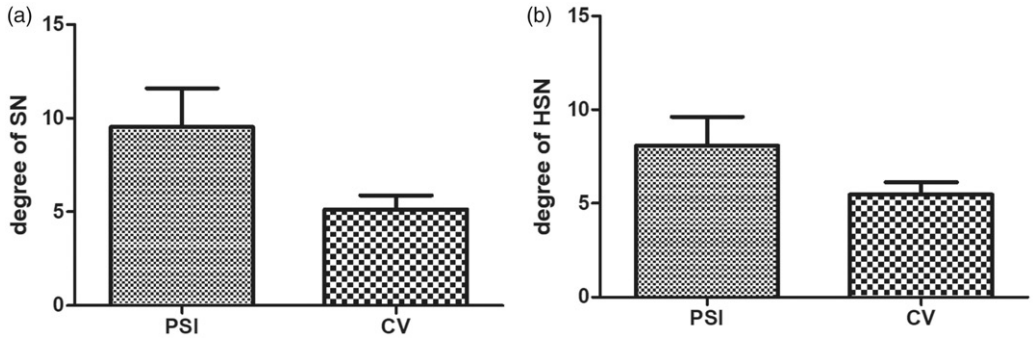

Figure 1. Videonystagmography data of the persistent static imbalance (PSI) group and control vestibulopathy (CV) group. The degree of spontaneous nystagmus (SN) (A) and head-shaking nystagmus (HSN) (B) was larger in the PSI group, but without significance.

Table 2. Comparison of averaged canal paresis of caloric test between groups.

	PSI group ($n = 13/17$)	CV group ($n = 22/30$)	p value (Independent t-test)
Canal paresis (±SD)	37.38 (±33.04)	40.67 (±23.42)	.733

Table 3. Abnormal caloric test rate of both groups.

	PSI group ($n = 13/17$)	CV group ($n = 22/30$)
Normal (<25%)	7 (53.8%)	5 (22.7%)
Abnormal (≧25%)	6 (46.2%)	17 (77.3%)

PSI: persistent statistic imbalance.
CV: control vestibulopathy.

= 33, $p = .733$) (Table 2). The PSI group showed a 46.2% abnormal rate and the CV group showed a 77.3% abnormal rate; the difference was not significant (Fisher's exact test: $p = .079$) (Table 3).

The SHA parameters (part of the RCT) were analyzed. Gain values did not show any difference between the groups at any frequency [(0.04 Hz, Man–Whitney test: $U = 145$, $p = .06$) (0.16 Hz, Man–Whitney test: $U = 169$, $p = .18$) (0.64 Hz, independent t-test: $t = 0.1552$, df = 25, $p = .87$)] (Figure 2(A)). Asymmetry was greater in the PSI group at 0.04 Hz compared to the CV group, but not in any of the other frequencies [(0.04 Hz, Man–Whitney test: $U = 120.5$, $p = .02$) (0.16 Hz, Man–Whitney test: $U = 148$, $p = .09$) (0.64 Hz, Man–Whitney test: $U = 68.5$, $p = .96$)] (Figure 2(B)). A significantly increased phase lead was observed in the PSI group at 0.04 and 0.16 Hz, but not at 0.64 Hz [(0.04 Hz, independent t-test: $t = 4.449$, df = 40, $p < .001$) (0.16 Hz, Man–Whitney test: $U = 135$, $p = .04$) (0.64 Hz, Man–Whitney test: $U = 47.5$, $p = .22$)] (Figure 2(C)).

At all semicircular canals and both ears (ipsilesional [ipsi] and contralesional [contra]), the ratio of abnormal vHIT gain values did not significantly differ between the PSI and CV group (all tests, Fisher's exact test; anterior canal ipsi: $p = .209$, anterior contra: $p = .397$, lateral ipsi: $p = .115$, lateral contra: $p = 1.000$, posterior ipsi: $p = .053$, posterior contra: $p = .072$) (Table 4). There was no statistically significant difference of averaged ipsilesional gain value between PSI and CV group in each canal (independent t-test; anterior canal: $t = 2.03$, df = 30, $p = .051$; lateral canal: $t = 1.85$, df = 30, $p = .074$) (Man–Whitney test: posterior canal: $U = 58.00$, $p = .110$) (Table 5).

Discussion

Summary and interpretation of results

In the present study, we divided AUV patients into two groups, PSI and CV. We then compared the VFT outcomes. Considering the fact that the degree of nystagmus decreases over time, observation of larger nystagmus in the PSI group might suggest prolonged recovery, which could lead to the late disappearance of SN. However, a direct comparison of SN between the two groups failed to reveal any significant difference, suggesting that it is not the degree of SN that affects the late observation of SN. VFT results that reflect the dynamic imbalance of subjects such as HSN, the CP values of the caloric test, gain values of SHA, and vHIT interpretation failed to mark the difference between the two groups, leading us to predict that initial dynamic imbalances do not affect the poor recovery of static imbalance. Notably, among the SHA outcomes, low-frequency asymmetry and low/mid-frequency phase values were significantly different between the groups. In the PSI group, the initial low-frequency asymmetry value was higher and the phases (lead) at low and mid frequencies were also higher. Through these results, we can anticipate that when the initial SHA shows a larger asymmetry and a big phase lead, there is a greater chance that the patient could show SN at a later stage. SN at a later stage of the disease and delayed compensation of static imbalance could eventually lead to persistent symptoms at a later stage, at which point the majority of patients recover from the disease, leading to social and financial loss to the patient.

If we look at the data of current study in detail, there is a unique frequency specific finding of SHA result. Phase leads did show a difference between PSI and CV group at low and mid frequencies but at high frequency (0.64 Hz) there is no difference between groups. In fact, this result matches with the result from vHIT results (Table 3) showing no statistical difference of abnormal findings rate between two groups. Since vHIT reflects the high-frequency function around 3–5 Hz [10], it seems that these features (phase lead) among PSI is limited to the low-frequency area. Plausible reason for lack of low-frequency compensation can be the rehabilitation strategies during the daily life, which is high frequency.

Although there is no difference observed in the present study, persistence of dynamic imbalance which should be

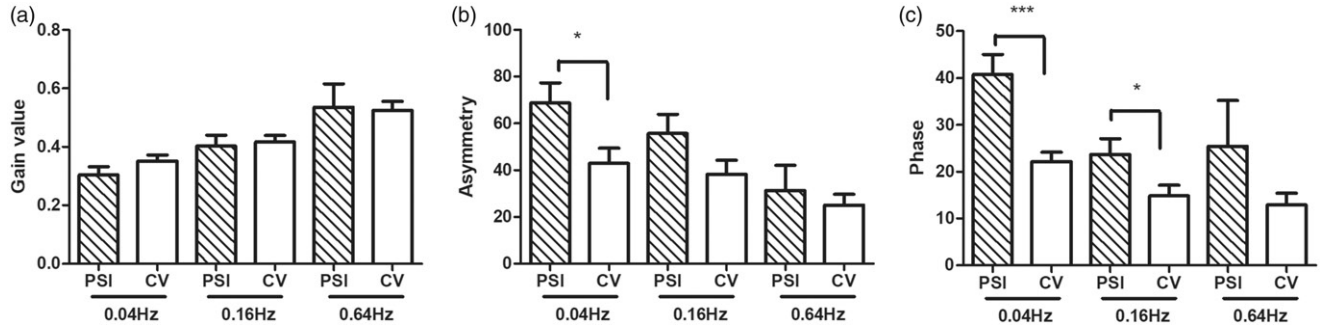

Figure 2. Parameters of the slow harmonic acceleration (SHA) test in both groups. (A) There was no significant gain difference between the PSI and CV group at any frequency. (B) Only a statistically increased asymmetry at 0.04 Hz was observed in the PSI group. (C) At 0.04 and 0.16 Hz, increased phase lead was observed in the PSI group, but not at 0.64 Hz. $^{*}p < .05$ and $^{***}p < .001$.

Table 4. Abnormal video head impulse (vHIT) test rate of both groups.

	Ipsilesional		Contralesional	
Location	PSI group ($n = 11/17$)	CV group ($n = 21/30$)	PSI group ($n = 11/17$)	CV group ($n = 21/30$)
Anterior semicircular canal				
Normal (>0.6)	1 (9.1%)	7 (33.3%)	7 (63.6%)	17 (80.9%)
Abnormal (≦0.6)	10 (90.9%)	14 (66.7%)	4 (36.4%)	4 (19.1%)
Lateral semicircular canal				
Normal (>0.8)	1 (9.1%)	8 (38.1%)	8 (72.7%)	15 (71.4%)
Abnormal (≦0.8)	10 (90.9%)	13 (61.9%)	3 (27.3%)	6 (28.6%)
Posterior semicircular canal				
Normal (>0.6)	4 (36.4%)	16 (76.2%)	4 (36.4%)	15 (71.4%)
Abnormal (≦0.6)	7 (63.6%)	5 (23.8%)	7 (63.6%)	6 (28.6%)

PSI: persistent statistic imbalance.
CV: control vestibulopathy.

Table 5. Comparison of averaged gain value of ipsilesional video head impulse test (vHIT) between groups.

	PSI group ($n = 11/17$)	CV group ($n = 21/30$)	p value
Anterior semicircular canal	0.34 (±0.25)	0.55 (±0.28)	.051†
Lateral semicircular canal	0.45 (0.28)	0.70 (0.40)	.074†
Posterior semicircular canal	0.54 (±0.13)	0.68 (±0.18)	.110‡

†Independent *T*-test.
‡Mann–Whitney test.

noted by vHIT and HSN should be reevaluated using further analytic methods. HSN documentation failure which was mentioned above might have affected the final outcome, and more detailed analytic methods for vHIT [11] may also be very useful comparing the result of two groups. Higher rate of normal caloric response in PSI group, although the statistics failed to show significance due to a low number of subject, may suggest an additional theory for disease progression. As reported before [12], conversion of normal to unilateral canal paresis occurs and these normal caloric cases might be slow converters and could show slow disease process and lead to prolonged recovery. To elucidate this hypothesis, serial caloric response analysis should be performed.

Relationship between phase lead and static imbalance

Phase lead is one of the important parameters determining the disease stage of AUV. In the acute stage of AUV, a decrease in gain, asymmetry to the lesion side, and phase lead are observed with the SHA test. However, these features or results do not last long. When patients recover (partially) by compensation, the gain increases and asymmetry normalizes to a symmetric level. Phase leads also trim down to a normal value, but this is known to be sustained for longer than gain and symmetry normalization. Therefore, if there is some loss of gain and no asymmetry with phase lead, we could predict a partially compensated or recovered vestibular function after AUV, as long as the patient's disease course corresponds to that of AUV.

One of the important structures that are responsible for the compensation of static imbalance is that of the commissural inhibitory system [13,14]. This functionally inhibitory commissural system integrates and connects the bilateral vestibular nucleus to achieve paired (push and pull) activity of bilateral vestibular end organs and establishes dynamic responsiveness and sensitivity to head movement [14,15]. This connection by the commissural system is responsible for the severe symptoms of AUV at the initial stage; the lack of input from the ipsilesional vestibular periphery is insufficient to cause static imbalance on its own and, therefore it needs combining with paired inhibition of the lesioned vestibular nucleus via the inhibitory commissural pathway from the contralesional side [14]. Furthermore, change (down-regulation) of this commissural response is thought to be one of the fast-acting compensatory mechanisms for static imbalance [14,16]. After a short duration of very severe imbalance caused by the loss of function and further inhibition from the contralateral nucleus, commissural inhibition is down-regulated to reduce the asymmetry of the two vestibular nuclei, leading to the stabilization of static imbalance.

Change of the time constant (velocity storage) after disruption of the commissural system has been documented in several previous reports [16–19]. Phase lead, which was observed to be larger in the PSI group in the present study, is very closely related to the time constant; a larger phase lead indicates a shorter time constant and lack of a velocity storage system [20]. The larger phase lead observed in the experimental group could result from severe depletion of the velocity storage system driven by disruption of the commissural system at the initial time point. To achieve static compensation after vestibulopathy, the commissural system

has to be involved to a certain degree, as discussed above. However, slower compensation is expected due to expected disruption of the commissural system, as evidenced by the phase lead (depleted time constant) observed in the current study. Since it is very difficult to confirm this theory by histology, imaging studies to identify the connectivity between the brain subunits or hemisphere might be useful and necessary to prove the disrupted connectivity between hemispheres in PSI subjects.

Clinical application

Predicting the poor recovery of static imbalance would be the first step in further classifying patients and applying therapeutics using different approaches. For example, if the patient has a high phase lead at the initial stage they could be prescribed activities that could adapt or substitute static compensation more aggressively. Since it is unclear which mechanistic pathway of compensation is affected (a theory of disrupted commissural interaction or similar could be speculated), clarifying the underlying mechanism using animal models or imaging studies would be necessary, as would a larger sized study to confirm the time constant changes in PSI patients.

Disclosure statement

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ORCID

Jae Yun Jung http://orcid.org/0000-0002-1870-0748
Min Young Lee http://orcid.org/0000-0002-6860-8042

References

[1] Brandt T, Dieterich M, Strupp M. Vertigo and dizziness. Springer-Verlag London Limited. 2005.
[2] Sekitani T, Imate Y, Noguchi T, et al. Vestibular neuronitis: epidemiological survey by questionnaire in Japan. Acta Oto-Laryngologica. 1993;113:9–12.
[3] Adamec I, Krbot Skoric M, Handzic J, et al. Incidence, seasonality and comorbidity in vestibular neuritis. Neurol Sci. 2015; 36:91–95.
[4] Arbusow V, Schulz P, Strupp M, et al. Distribution of herpes simplex virus type 1 in human geniculate and vestibular ganglia: implications for vestibular neuritis. Ann Neurol. 1999;46: 416–419.
[5] Theil D, Derfuss T, Strupp M, et al. Cranial nerve palsies: herpes simplex virus type 1 and varizella-zoster virus latency. Ann Neurol. 2002;51:273–274.
[6] Strupp M, Magnusson M. Acute unilateral vestibulopathy. Neurol Clin. 2015;33:669–685.
[7] Lacour M, Helmchen C, Vidal PP. Vestibular compensation: the neuro-otologist's best friend. J Neurol. 2016;263:54–64.
[8] Kim CH, Na BR, Park HJ, et al. Impairment of static vestibular function is limited in patients with sudden sensorineural hearing loss with vertigo. Audiol Neurotol. 2013;18:208–213.
[9] Choi KD, Oh SY, Kim HJ, et al. Recovery of vestibular imbalances after vestibular neuritis. Laryngoscope. 2007;117:1307–1312.
[10] Petrak M, Bahner C, Beck D. Video head impulse testing (vHIT): VOR analysis of high frequency vestibular activity. Hear Rev. 2013.
[11] 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;135:886–894.
[12] Lee SU, Park SH, Kim HJ, et al. Normal caloric responses during acute phase of vestibular neuritis. J Clin Neurol. 2016;12: 301–307.
[13] Bergquist F, Ludwig M, Dutia MB. Role of the commissural inhibitory system in vestibular compensation in the rat. J Physiol. 2008;586:4441–4452.
[14] Olabi B, Bergquist F, Dutia MB. Rebalancing the commissural system: mechanisms of vestibular compensation. J Vestib Res. 2009;19:201–207.
[15] Arnold DB, Robinson DA. The oculomotor integrator: testing of a neural network model. Exp Brain Res. 1997;113:57–74.
[16] Graham BP, Dutia MB. Cellular basis of vestibular compensation: analysis and modelling of the role of the commissural inhibitory system. Exp Brain Res. 2001;137:387–396.
[17] Dieterich M. Central vestibular disorders. J Neurol. 2007;254: 559–568.
[18] Katz E, Vianney de Jong JM, Buettner-Ennever J, et al. Effects of midline medullary lesions on velocity storage and the vestibulo-ocular reflex. Exp Brain Res. 1991;87:505–520.
[19] Wearne S, Raphan T, Cohen B. Contribution of vestibular commissural pathways to spatial orientation of the angular vestibuloocular reflex. J Neurophysiol. 1997;78:1193–1197.
[20] Clement G, Reschke MF. Relationship between motion sickness susceptibility and vestibulo-ocular reflex gain and phase. J Vestib Res. 2018;28:295–304.