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Mechanism of Paroxysmal Downbeat Central Positional Nystagmus

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Abstract

Mechanism of Paroxysmal Downbeat Central Positional Nystagmus

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Background: Central positional nystagmus (CPN) has increasingly attracted the attention of clinicians since it may mimick benign paroxysmal positional vertigo (BPPV). CPN is frequently associated with lesions involving the cerebellum or brainstem. CPN could be divided into paroxysmal and persistent forms according to its temporal characteristics. Recent works had provided some insights on the mechanisms of persistent and paroxysmal types of CPN respectively. Persistent CPN has been explained by erroneous neural processing within the velocity-storage circuit located in the brainstem and cerebellum that functions in estimating the angular head velocity, gravity direction, and inertial acceleration. While paroxysmal CPN was attributed to disinhibition and enhanced responses of the secondary

vestibular neurons during the positioning due to lesions involving the nodulus and uvula, the mechanism of paroxysmal CPN requires further exploration.

Purpose: To elucidate the mechanism of paroxysmal CPN by determining the effects of head rotation velocity on the intensity of paroxysmal downbeat nystagmus induced during straight head hanging (SHH).

Methods: We prospectively recruited 21 patients with paroxysmal downbeat CPN induced during SHH at the Dizziness Center of Seoul National University Bundang Hospital from September 2018 to July 2019. Twenty-one patients had manual SHH at two different lying velocities, the fast (routine) and slow, and they also underwent SHH at different rotation velocities of 10, 20, 30, and 40 °/s using a motorized rotation chair. Induced nystagmus was recorded using video-oculography and the maximum slow phase velocity (SPV) and time constant (TC) of the induced paroxysmal nystagmus were analyzed.

Results: During manual SHH, paroxysmal downbeat nystagmus was invariably induced during routine (fast) SHH. In contrast, paroxysmal downbeat nystagmus was absent or minimal during slow positioning. During motorized SHH, the median of maximum intensity of downbeat nystagmus increased from 7.6 °/s (0-16.9) to 14.0 °/s (0-32.5), 16.5 °/s (0-44.6), and 19.1 °/s (0-55.2) as the rotation velocity increased from 10 to 20, 30, and 40°/s ($P < 0.001$, $P < 0.001$, $P = 0.004$; linear mixed models). In contrast, the TCs of paroxysmal

downbeat CPN remained unchanged (P = 0.558, P = 0.881, P = 0.384, linear mixed models).

Conclusion: The dependence of nystagmus intensity on head rotation velocity supports a disinhibited and exaggerated inhibitory rebound of the canal signals as the mechanism of paroxysmal CPN.

Keyword: vertigo, nystagmus, central positional nystagmus, downbeat nystagmus, mechanism

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Chapter 1. Introduction

1.1. Study Background

1.1.1. Historical of Central Positional Nystagmus

Positional nystagmus (PN) refers to nystagmus induced when the head position changes in the direction of gravity.[4] PN was first described by Bàràny (1921), and he attributed it to a disorder of the otolithic organ.[4] Fromm and Nylen (1935)[27] observed PN after sarcoma implantation in the posterior cranial fossa in labyrinthectomy and labyrinth-intact animals. Seiferth (1937)[61] found that acute quinine intoxication in dogs produced PN, possibly of central origin. Nylén (1939)[56] described two types of PN in 279 out of 673 cases of brain tumors (230 posterior fossa tumors) and found that 90% of patients were posterior fossa tumors and 26% of patients were supratentorial neoplasms. Type 1 was direction-changing nystagmus, and type II was direction-fixed nystagmus. In 1950, Nylén classified and defined three main types of PN: direction-changing, direction fixed, and irregular.[57] He stated that both the peripheral and central disorders could lead to PN.[57] In 1952, Dix and Hallpike described the characteristics of benign paroxysmal positional vertigo (BPPV) and developed the diagnostic maneuver for posterior canal BPPV.[25] Several years later, Aschan et al. (1956) noted an important drawback in Nylén's classification, namely, that it did not consider whether nystagmus was persistent or transient

after head positioning.[3] Aschan et al. changed Nylen's classification of PN into persistent direction-changing, persistent direction-fixed, and transitory (paroxysmal) types. [3] Subsequently, PN was mostly named clinically following Aschan's classification. As we can see above, PN can be seen in both peripheral and central vestibular disorders, of which central positional nystagmus (CPN) accounts for approximately 12%.[48,50] CPN is frequently associated with lesions involving cerebellum and /or brainstem and because it may lead to the occurrence of malignant adverse events, CPN has increasingly attracted the attention of clinicians.[58]

1.1.2. Structural Lesions and Underlying Disease

CPN was more common in lesions involving the cerebellum (74.4%), such as nodulus, uvula, tonsil, inferior, middle and superior cerebellar peduncles[2,16,17,21,24,42,44], followed by the fourth ventricle (14.6%), isolated brainstem lesions (8.5%), and diffuse or nonspecific lesions(6.1%).[50] The reported causes of CPN include cerebellar strokes, cerebellar tumors[13], Chiari malformation[37], brainstem strokes[47], multiple sclerosis[1], multiple system atrophy[43], posterior fossa tumor[17], hereditary cerebellar ataxia[34,69], vestibular migraine[67], antiepileptic drug poisoning[18], heat stroke[16], X-linked adrenoleukodystrophy[35] and paraneoplastic. etc. [23,24]

1.1.3. Characteristics of CPN

The classification and features of CPN are summarized in Table 1.

According to the temporal characteristics of nystagmus, CPN could be divided into persistent and paroxysmal forms.[16] These two forms often coexist in a single individual patient, with an initial paroxysmal type, and gradually evolving into a persistent one.[16,17,24] CPN mostly takes the form of apogeotropic [15] or geotropic [21] nystagmus when the head is turned to either side while supine, or downbeat nystagmus (DBN) after lying down or straight head hanging.[14]

Persistent CPN is featured by persistent downbeat with head hanging or upright and apogeotropic or geotropic after head-turning to either side while supine. Persistent downbeat nystagmus usually increases in the prone position and decreases in the supine position.[54] A recent study compared the features of persistent apogeotropic CPN that arose from unilateral cerebellar injuries with persistent apogeotropic nystagmus caused by horizontal canal BPPV.[15] The study found that the intensity of spontaneous horizontal nystagmus did not differ between in upright position and in supine position in patients with unilateral cerebellar injuries, while it became more potent after changing from upright to supine position in patients with horizontal canal BPPV.[15] And after subtracting the spontaneous component while supine, the intensity of the apogeotropic component induced by turning the head to the right or left side while supine did not differ. For persistent geotropic CPN, the peak intensity and asymmetry of geotropic positional nystagmus were reported to be similar in those with unilateral cerebellar lesions and with presumed light cupula.[21]

Paroxysmal CPN is featured by transient geotropic or apogeotropic

nystagmus after head-turning to either side while supine, and upbeat or downbeat nystagmus after lying down, straight head hanging (SHH) or sitting up.[24] The direction of paroxysmal CPN may occasionally reverse while maintaining head position.[16] Of those, paroxysmal DBN while lying down or SHH is most common.[16] Paroxysmal upbeat CPN induced by SHH and/or Dix-Hallpike maneuvers, and paroxysmal geotropic nystagmus induced by Pagnini-McClure maneuvers have rarely been reported.[24,29,46] The intensity of paroxysmal downbeat CPN is peak at its onset or within 3-5s of its onset, usually along with severe vertigo, and then decreases exponentially.[16] The time constant (TC) of paroxysmal downbeat CPN is about 4-6s, and is similar to that of the cupula in the vertical semicircular canals or that of the velocity-storage (VS) for the vertical rotational vestibulo-ocular reflex (VOR).[16] Meanwhile, paroxysmal positional downbeat nystagmus may also be caused by an apogeotropic variant of posterior canal BPPV[51,64] or anterior canal BPPV[66]; and paroxysmal positional upbeat nystagmus may also be caused by canalolithiasis of the posterior canal.[51] Paroxysmal geotropic nystagmus may also be caused by canalolithiasis of the horizontal canal.[59] But the slow phase velocity of the nystagmus mentioned above often showed a crescendo-decrescendo pattern.[65] This phenomenon could be used to differentiate paroxysmal CPN which peaks at its onset from benign paroxysmal positional nystagmus (BPPN). In addition, the effect of canalith repositioning therapy also helps to differentiate paroxysmal CPN from BPPN.[49] The remission of the vertigo and nystagmus after the application of the canal-specific

canalith repositioning therapy may be supportive of the diagnosis of BPPV.[12,15,38,39,41,51]

1.1.4. Mechanism of CPN

Persistent CPN has been explained by erroneous neural processing within the velocity-storage circuit located in the brainstem and cerebellum that functions in estimating the angular head velocity, gravity direction, and inertial acceleration.[15] The mechanism of paroxysmal CPN requires further exploration. In our previous study, the paroxysmal form of CPN mainly occurred in the planes of semicircular canals inhibited during the positioning and showed the features suggestive of a semicircular canal origin regarding the latency, duration, direction, and time constant of nystagmus.[16] Most patients with paroxysmal CPN from a circumscribed lesion showed an involvement of the nodulus or uvula.[16] Based on those findings, paroxysmal CPN was attributed to disinhibition and enhanced responses of the secondary vestibular neurons during the positioning due to lesions involving the nodulus and uvula.[16] This is supported by an experimental study that observed paroxysmal DBN during positioning after removal of the nodulus and uvula.[26] In this instance, increment of the post-rotatory signals is invoked to generate paroxysmal CPN.[16] For example, paroxysmal DBN observed during lying down or SHH is explained by transient over-activation of the anterior and/ or horizontal canals on both sides.[16] According to this explanation, We speculated that the intensity of paroxysmal CPN would

depend on stimulation intensity of the semicircular canals during the positioning, and thus lying velocity (acceleration) in paroxysmal downbeat CPN.

1.2. Purpose of Research

This study aimed to determine the effect of lying (head rotation) velocity (acceleration) on the intensity of paroxysmal downbeat CPN induced during SHH by adopting a stepwise increase in the rotation velocity. We hypothesized that the intensity of induced nystagmus would increase in proportion to the lying velocity.

1.3. Publication Arising from This Thesis

Ling X, Kim HJ, Lee JH, Choi JY, Yang X, Kim JS. Positioning Velocity Matters in Central Paroxysmal Positional Vertigo: Implication for the Mechanism. Front Neurol. 2020 Oct 22;11:591602. doi: 10.3389/fneur.2020.591602. PMID: 33193058; PMCID: PMC7643012.

1.4. Publication Not Included in This Thesis

Ling X, Kim HJ, Lee JH, Choi JY, Yang X, Kim JS. Diagnostic Value of Straight Head Hanging in Posterior Canal Benign Paroxysmal Positional Vertigo. J Clin Neurol. 2021 Oct;17(4):558-562. doi: 10.3988/jcn.2021.17.4.558. PMID: 34595864; PMCID: PMC8490902.

Chapter 2. Materials and methods

2.1. Patients

We prospectively recruited 27 patients with paroxysmal downbeat CPN at the Dizziness Center of Seoul National University Bundang Hospital from September 2018 to July 2019. All experiments followed the tenets of the Declaration of Helsinki and this study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB No. B-1908/558-103).

All patients underwent detailed neuro-otologic evaluation by the senior author (J.S.K). The diagnosis of paroxysmal downbeat CPN was based on (1) paroxysmal downbeat nystagmus (< 1 minute) induced during SHH, (2) presence of other symptoms and signs indicative of brainstem or cerebellar dysfunction, or brainstem or cerebellar lesions documented on MRIs, and (3) no resolution of paroxysmal downbeat nystagmus with repeated canalith repositioning maneuvers for benign paroxysmal positional vertigo involving the anterior semicircular canals. Of the 27 patients, 21 (12 men, mean age ± SD = 54.4 ± 14.9 years) were finally included for analyses after excluding six patients due to (1) a duration of the paroxysmal nystagmus less than five seconds (n=1), (2) concomitant periodic alternating nystagmus that interfered accurate analyses of downbeat nystagmus (n=1), (3) an inconsistency; direction-

changing or alternating with horizontal nystagmus (intermittent, n=2), and (4) incomplete evaluation (n=2).

2.2. Oculography

Eye movements were recorded binocularly using 3-dimensional video-oculography (VOG, SLVNG®, SLMED, Seoul, South Korea). Spontaneous nystagmus was recorded both with and without visual fixation in the sitting position. Gaze-evoked nystagmus, horizontal smooth pursuit, horizontal and vertical saccades, and horizontal head-shaking nystagmus were also evaluated. Gaze test: The patient sits on a chair, and the eyes are about 1.2 meters away from the target. The patient was instructed to look at the target displaced horizontally (30°) and vertically (15°) without the head motion. If nystagmus was induced, record the direction of nystagmus and slow phase velocity.[32] Gaze-evoked nystagmus was considered to be present when the nystagmus beats in the direction of gaze bilaterally.[32] Saccade test: Horizontal and vertical saccades were generated by instructing the patient to follow a moving target on a light bar located 1.2 m away from where they sat, and the target amplitudes were fixed at ±15° and ±30°. For each saccade, the latency, velocity, and accuracy were computed. Head shaking test: Instruct the patient to sit upright on a chair with the head tilted forward about 20° to bring the horizontal semicircular canal into the plane of stimulation, and the examiner holds the patient's head while shaking the patient's head horizontally to the left and right for 15

seconds, with an amplitude of about 20° and a frequency of 2-3 Hz. Start recording after shaking the patient's head, instruct the patient to open his eyes after stopping shaking his head, and record for at least 1 min. Observe whether nystagmus occurs. If nystagmus occurs, record the direction, duration, and slow phase velocity of nystagmus.[19,31,32] Smooth pursuit (SP) test: The patient sits on a chair, the head is fixed in the neutral position, and the eyes are about 1.2 meters away from an illuminated red target. The red target moves along a sinusoidal trajectory with peak velocities of 10°/s and 20°/s.[36] After eliminating saccades detected based on the velocity threshold criterion (100°/s), smooth pursuit gain was determined as the ratio of peak eye velocity to peak target velocity.[36]

2.3. Positioning maneuvers

All patients had manual SHH at both fast (routine) and slow lying velocities. During the fast SHH, patients were laid from the sitting position onto the lying down position with the head extended about 30 degrees below the table. During the fast SHH, this positioning was performed at a routine velocity and was completed usually within three seconds (two to four seconds). Thus, the mean head rotation velocity was about 40°/s during the fast SHH test. During the slow SHH, the patients assumed the same position over about 35 seconds (from 25 to 51 seconds) with an assistance by the examiner. Thus, the mean head rotation velocity was approximately 3-4 °/s during the slow SHH

(Figure. 1).

All patients also underwent SHH at different rotation velocities of 10, 20, 30, and 40 °/s using a 3-dimensional motorized rotation chair (SLRVT®, SLMED, Seoul, South Korea, Figure.2). During this maneuver, the patients were tilted backward 100° from the sitting position without extending the neck at each rotation velocity.

In each testing condition, the SHH position was maintained until the positional nystagmus disappeared or at least for one minute. The positional nystagmus was recorded at a sampling rate of 120 Hz without visual fixation in darkness using video-oculography (VOG, SLVNG®, SLMED, Seoul, South Korea).

2.4. Analyses of nystagmus

Digitized eye position data were analyzed with MATLAB software (version R2019b, The MathWorks, Inc., MA, USA). For each paroxysmal CPN, the intensity (maximum slow phase velocity, SPV) and time constant (TC) were calculated. When persistent CPN was combined with the paroxysmal one, we calculated the maximum SPV and TC of paroxysmal CPN after subtracting the persistent component from the velocity profile of induced positional nystagmus.

2.5. Statistical analysis

Statistical analyses were performed using SPSS software (version

20.0, IBM SPSS Statistics, N.Y., USA). Continuous variables were expressed as a mean ± SD for parametric values or as a median (range) for nonparametric ones. Counting variables were expressed as a percentage. Normality of the data was determined using the Shapiro-Wilk test. Linear mixed model analysis was used to determine any difference in the maximum SPV and TC of paroxysmal downbeat CPN among the test conditions that had adopted different rotation velocities using a motorized rotation chair. The level of statistical significance for the linear mixed model analyses was corrected using the Bonferroni method, and the corrected level of significance was set at 0.0083 (0.05/6) since the comparisons were performed six times in each group. The Wilcoxon signed ranks test were used to determine any difference in the maximum SPVs of paroxysmal downbeat CPN induced during the fast and slow SHH and maximum SPVs of paroxysmal downbeat CPN induced during the fast SHH and motorized positioning test at a rotation velocity of 40.0°/s, and the paired t-test was used to determine any difference in the TCs of paroxysmal downbeat CPN induced during the fast SHH and motorized positioning test at a rotation velocity of 40.0 °/s. The significance threshold was set at a 2-sided P value less than 0.05.

Chapter 3. Results

3.1. Clinical characteristics

Underlying disorders included cerebellar ataxia (n = 7), spinocerebellar ataxia (n = 6), episodic ataxia (n = 4), Chiari malformation (n = 1), multiple system atrophy-cerebellar subtype (n = 1) and no etiology was identified in the remaining two patients.

During visual fixation, eight patients (38.1%) showed spontaneous nystagmus that was pure downbeat in seven, and mixed horizontal and downbeat in the remaining one. The SPV of downbeat nystagmus ranged from 0.7 to 8.2°/s (median = 2.0). Without visual fixation in darkness, 15 patients (71.4%) showed spontaneous nystagmus that was pure downbeat in eight, mixed horizontal-downbeat in five, pure horizontal in one, and mixed horizontal-upbeat in the remaining one. The SPV of downbeat nystagmus ranged from 1.1 to 8.7°/s (median = 3.1) without visual fixation in darkness. After horizontal head-shaking, 18 patients (85.7%) showed nystagmus that was mixed horizontal-downbeat in 11, pure downbeat in five, and pure horizontal in two. Gaze-evoked nystagmus was found in 14 patients (66.7%), and eight of them also showed rebound nystagmus. Horizontal smooth pursuit was impaired in 14 patients (66.7%). Horizontal saccades were abnormal in 11 patients (52.4%); hypermetric in six, hypometric in four, and hypometric and slow in one (Table 2).

3.2. Manual SHH

All 21 patients showed paroxysmal downbeat CPN during the routine (fast) positioning, and only two of them showed downbeat nystagmus during the slow SHH (Table 3). During the routine SHH, the downbeat CPN was pure paroxysmal in 16 and mixed paroxysmal and persistent in five patients. The paroxysmal downbeat CPN showed a peak initially in 19 patients (90.5%) and reached its peak within 2.5 seconds in the remaining two. After then, the nystagmus decreased exponentially. The maximum SPV of positional downbeat nystagmus ranged from 4.6 to 65.6°/s (median = 19.8, mean ± SD = 23.4 ± 14.7), and the TC ranged from 1.1 to 7.4 seconds (median = 3.5, mean ± SD = 3.8 ± 1.8) during the fast SHH. During the slow SHH, the maximum SPVs for the two patients with discernable positional downbeat nystagmus were 10.4 and 12.3°/s with the TCs at 1.3 and 3.7 seconds. Thus, there was a significant rise in the maximum SPV of paroxysmal downbeat CPN as the lying velocity increased (Z = -4.02, Wilcoxon signed ranks test, P < 0.001, (Table 3, Figure. 3).

3.3. Motorized rotation chair test

The median of maximum SPV of paroxysmal downbeat CPN was 7.6 °/s (range: 0-16.9; mean ± SD = 7.2 ± 5.7) at the rotation velocity of 10°/s, which increased to 14.0 °/s (range: 0-32.5; mean ±

SD =14.6 ± 8.1) at 20°/s, 16.5°/s (range: 0-44.6; mean ± SD = 17.6 ± 9.5) at 30°/s, and 19.1°/s (range: 0-55.2; mean ± SD = 20.5 ± 12.1) at 40°/s. Thus, there was a significant rise in the maximum SPV of paroxysmal downbeat CPN as the lying velocity increased [(95% CI, -18.42 to -8.19), $P < 0.001$; (95% CI, -8.95 to -3.00), $P < 0.001$; (95% CI, -4.84 to -1.06), $P = 0.004$; Linear mixed model; Figure. 4A]. In contrast, the TCs of paroxysmal downbeat nystagmus remained at about 3.5 seconds without a difference among the four testing conditions [(95% CI, -1.12 to 0.62), $P = 0.558$; (95% CI, -0.51 to 0.60), $P = 0.881$; (95% CI, -0.29 to 0.70), $P = 0.384$, Linear mixed model, Figure. 4B].

Six patients showed both paroxysmal and persistent components of positional nystagmus, and the persistent nystagmus was upbeat (0.2-3.1°/s) in five and downbeat (3.1°/s) in one.

3.4. Comparison of manual and motorized SHH

We compared the maximum SPVs and TCs of the paroxysmal downbeat nystagmus between the manual fast SHH and motorized SHH test at the rotation velocity of 40 °/s since the head rotation velocities were similar for those testing conditions, and found that the maximum SPVs [19.1 (0-55.2) versus 19.8 (4.6-65.6) °/s, $Z = -1.06$, Wilcoxon signed ranks test, $P = 0.29$] and TCs [3.8 ± 1.9 versus 3.4 ± 1.6 seconds, (95% CI, -0.02 - 0.92), paired t-test, $P = 0.06$] (Figure 5) of the paroxysmal downbeat CPN induced during both tests were similar.

Chapter 4. Discussion

We found that the intensity of paroxysmal downbeat CPN during SHH depends on the rotation velocity (acceleration) of the head during the positioning while the TC was not affected by the rotation velocity. Furthermore, the intensity of positional downbeat nystagmus increases in proportion to the positioning velocity during the motorized rotatory chair tests.

Previous studies described two types of CPN, the paroxysmal and persistent, even though the underlying pathologies were similarly located in the cerebellum, mostly in the nodulus and uvula.[16] In this study, most patients showed diffuse cerebellar dysfunction in association with the hereditary or acquired forms of ataxia. However, most of our patients with paroxysmal CPN also showed neurological signs indicating dysfunction of the vestibulocerebellum which included spontaneous downbeat nystagmus, gaze-evoked nystagmus, perverted head-shaking nystagmus, hypometric and hypermetric saccades, and impaired smooth pursuit.[32,33,60] Since these ocular motor findings cannot be explained by BPPV, detailed ocular motor examinations could be attributed to differentiate paroxysmal CPN from BPPN.

In this study, the intensity of paroxysmal downbeat CPN induced during SHH depended on the positioning velocity during either manual SHH or the whole-body rotation using a motorized chair. Indeed, most

patients showed no or minimal downbeat nystagmus during SHH when the positioning was performed at a very slow speed. This was also observed in a previous study on spontaneous downbeat nystagmus even though the detailed findings or mechanisms were not explored.[7] In this study, the TCs of paroxysmal downbeat CPN remained similar at about 3.5 seconds among the different testing conditions, which are similar to the TCs of the vertical semicircular canals.[9,10,55] These characteristics of paroxysmal downbeat nystagmus observed in this study are consistent with those found in our previous study on paroxysmal CPN regarding its maximum at onset, short duration with a TC around four seconds, and alignment of the nystagmus direction with the vector sum of the rotational axes of the semicircular canals that are normally inhibited during the positioning.[16] Based on these findings, we previously proposed that paroxysmal CPN is generated by disinhibition and enhanced responses of the secondary vestibular neurons during positioning due to cerebellar dysfunction.[16] The similar TCs regardless of different nystagmus intensity in each testing condition are consistent with the findings observed in previous studies on the attenuation of nystagmus but constant TC during rotations having adopted a stepwise increase in the head rotation velocity.[62,63]

The first-order neurons from the horizontal semicircular canal have a resting discharge and the firing rate increases during head rotation that induces an ampullopetal flow of the endolymph and decreases during head motion that produces an ampullofugal flow of the endolymph. The reverse holds for the vertical semicircular canals.[5,28]

Within a specific dynamic range, this increase or decrease of action potentials is directly proportional to the magnitude of head acceleration or deceleration.[28] The primary vestibular afferents are classified into regular and irregular types according to their discharge properties.[28] The irregular afferents are related to the adaption response and the velocity-storage mechanism. The adaption response reflects two aspects of the unit's discharge. The first is a response decline to prolonged acceleration during both excitatory and inhibitory accelerations. The second is the secondary phenomenon in which the discharge declines rapidly and reverses its direction when it goes below the resting rate and gradually returns to the resting level in an approximately exponential fashion during the recovery period.[28] We speculated that the lesions involving vestibulocerebellum disinhibit the irregular afferents and result in the exaggerated post-acceleratory secondary phenomenon.[16] The function of the velocity-storage mechanism is to estimate the gravitational direction which integrates the rotation cues from the semicircular signals, and there is a rotation feedback loop inside the velocity-storage mechanism, which used to adjusts the estimated gravitational direction to real gravitational direction.[16] Lesions involving the vestibulocerebellum will disinhibit the irregular afferents and cause an exaggerated post-acceleratory secondary response, and lead to a big difference between the estimated gravitational direction and the real gravitational direction which leads to the post-rotatary nystagmus.[16] During SHH, the irregular vestibular fibers from both posterior semicircular canals are

mostly activated and this activation is followed by transient inhibitory rebound (post-acceleratory secondary phenomenon).[28] When this secondary inhibition becomes prominent due to dysfunction of the vestibulocerebellum, the exaggerated inhibitory signals conveyed to the vestibular storage mechanism may generate nystagmus through the rotational feedback mechanism.[16] In this scenario, the degree of post-acceleratory depression would depend on the strength of head acceleration during positioning, which forms the basis of this study. Indeed, the intensity of paroxysmal downbeat CPN induced during SHH depended on the positioning head velocity.

Several studies showed that transient compression of the vertebral arteries during neck rotation or extension may reduce the blood supply to the peripheral or the central parts of the vestibular system and give rise to paroxysmal downbeat nystagmus along with vertigo and tinnitus.[20,53,70] The presumed mechanism was excitation of unilateral or bilateral anterior semicircular canals.[20,53,70] Thus, paroxysmal downbeat nystagmus may be induced by head extension during SHH. However, in our study, only two patients (9.5%) showed paroxysmal downbeat CPN during the manual slow SHH test, and all patients showed paroxysmal downbeat CPN during the SHH using a rotation chair, which did not allow any neck motion during the positioning. Thus, the role of head extension, if any, in generating paroxysmal downbeat nystagmus could have been minimal in our study.

Four patients showed an evolution of initial positional downbeat into upbeat nystagmus over four to fifteen seconds. This reversal in the

direction of induced nystagmus is observed in various conditions including benign paroxysmal positional vertigo[6,22,45], head-shaking nystagmus[30], caloric stimulation[11], and vertebral artery occlusion syndrome[20], and may be ascribed to short-term adaption of the vestibular imbalance.

There are several limitations in our study. First, we only quantified paroxysmal downbeat CPN, and did not include other types of paroxysmal CPN such as geotropic or apogeotropic horizontal nystagmus during head turning to either side while supine. However, our observation was also similar in apogeotropic CPN. Second, for the patient's safety, we set the maximum rotation velocity at 40 °/s during motorized chair rotation. Thus, the characteristics of paroxysmal CPN during the head rotation at higher velocities remain to be determined. Third, due to severe vertigo, some patients involuntarily closed their eyes just after the positioning, and this might have biased the maximal SPV and TC. Fourth, we couldn't measure the accurate acceleration and deceleration of the head movement during the SHH tests, so it was not possible to further elucidate the effects of velocity and acceleration on paroxysmal CPN. Finally, we did not set up a normal control group. According to previous reports, the occurrence of PN in healthy controls was described as between 22.5 – 88%.[68] The intensity of vertical PN was mostly less than 6.48°/s, and the paroxysmal type of PN is less common in healthy subjects.[52] Some scholars even argued that PN only occurs in the presence of peripheral or central vestibular dysfunction, reflecting perhaps some degree of ischemia of the caudal

brainstem or cerebellum or an actual mass lesion in these areas.[8,40] In this study, most patients showed stronger (mostly > 10°/s) and paroxysmal CPN during the routine SHH test, which did not accord with the characteristics of physiological PN.

Chapter 5. Conclusion

This study revealed that the intensity of positional downbeat nystagmus increases in proportion to the positioning velocity (head rotation velocity) while the TC was not affected by the rotation velocity supports a disinhibited and exaggerated inhibitory rebound of the canal signals as the mechanism of paroxysmal CPN. The characteristics of CPN and associated ocular motor findings could be used to differentiate central from peripheral positional nystagmus.

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Figure legend and Figures

Figure 1. Recording of paroxysmal downbeat nystagmus during manual straight head hanging in patient 21. With slow positioning, no discernable nystagmus was induced, and the pre-existing spontaneous downbeat nystagmus was even suppressed. During fast positioning, in contrast, paroxysmal downbeat nystagmus was induced for several seconds. Only the vertical eye motion is presented and the shaded areas in pink indicate the period of positioning. Upward deflection denotes upward eye motion in each recording.

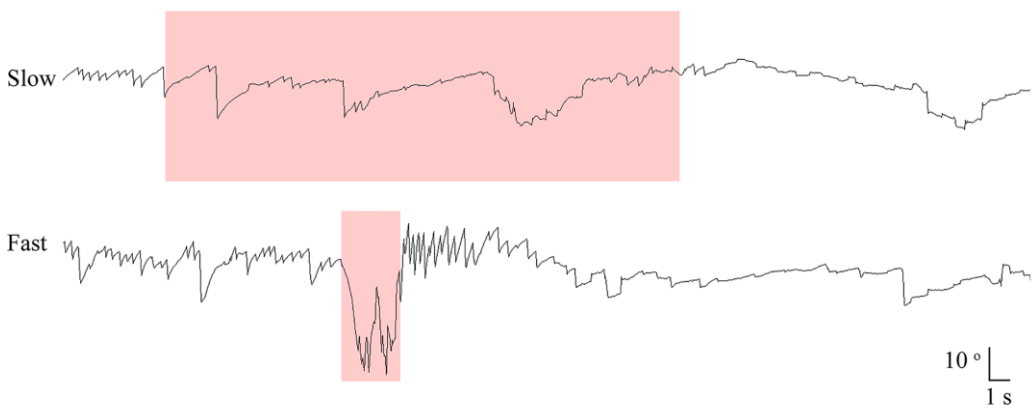


Figure 2. Recording of paroxysmal downbeat nystagmus induced during motorized rotation chair test at four different rotation velocities in patient 21. The intensity of induced downbeat nystagmus increased as the rotation velocity was escalated from 10 to 40°/s. The paroxysmal downbeat nystagmus was followed by a small upbeat nystagmus. Only the vertical eye motion is presented and the shaded areas in pink indicate the period of positioning. Upward deflection denotes upward eye motion in each recording.

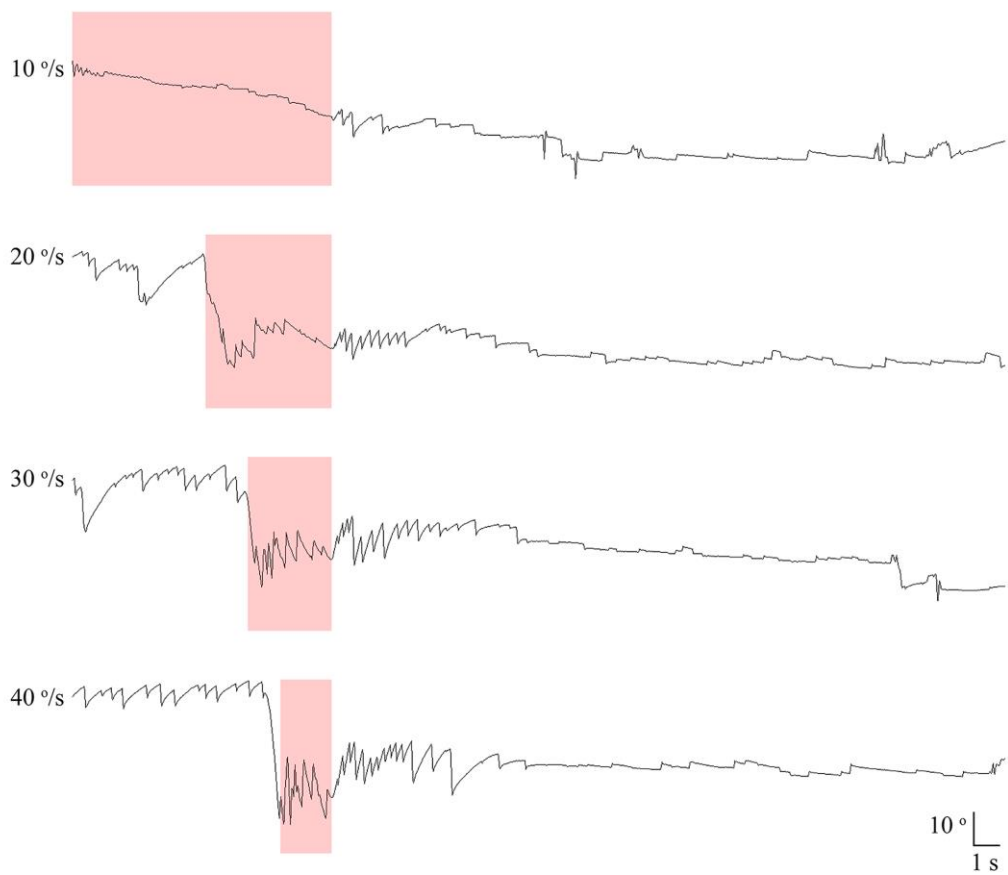
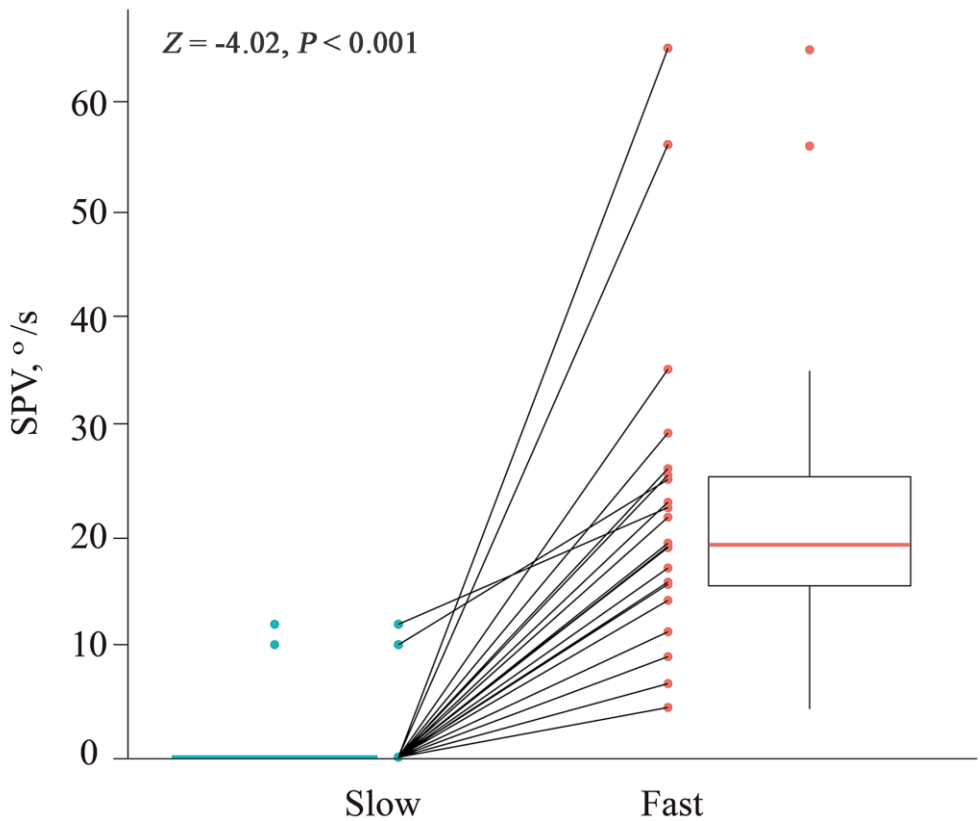


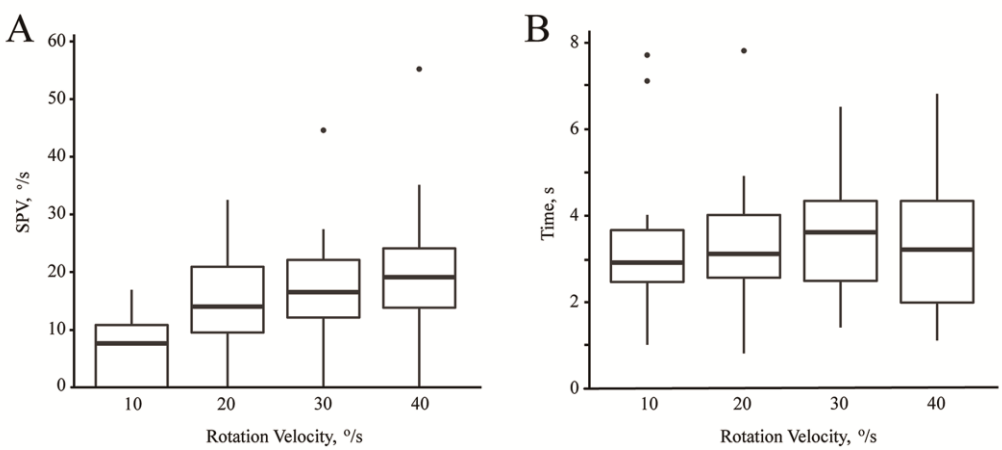
Figure 3. Comparison of the maximum slow phase velocity (SPV) of paroxysmal downbeat nystagmus induced during slow and fast manual straight head hanging tests in each patient.

During slow positioning, only two patients showed paroxysmal downbeat CPN, which became larger during fast positioning. In contrast, paroxysmal downbeat nystagmus was observed in all patients after fast positioning.



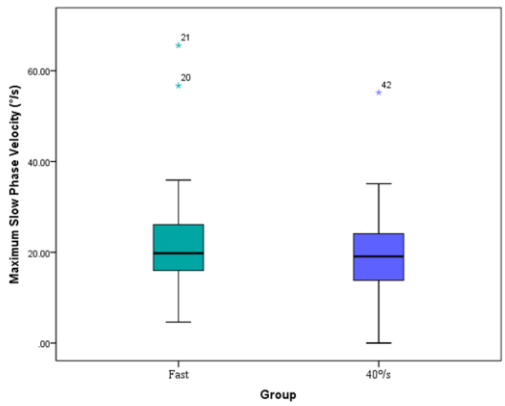
SPV, slow phase velocity

Figure 4. The maximum slow phase velocity (SPV, A) and time constant (B) of paroxysmal downbeat nystagmus induced during motorized rotation chair test at four different rotation velocities. As the rotation velocity was escalated from 10 to 40°/s, the maximum slow phase velocity of induced downbeat nystagmus increased while the time constant remained unchanged.



SPV, slow phase velocity

Figure 5. Comparison of the maximum slow phase velocity (SPV) and time constant of paroxysmal downbeat nystagmus induced during fast manual straight head hanging (SHH) and 40°/s of motorized SHH tests. There was no difference in maximum SPVs and time constant of induced downbeat nystagmus between two tests.



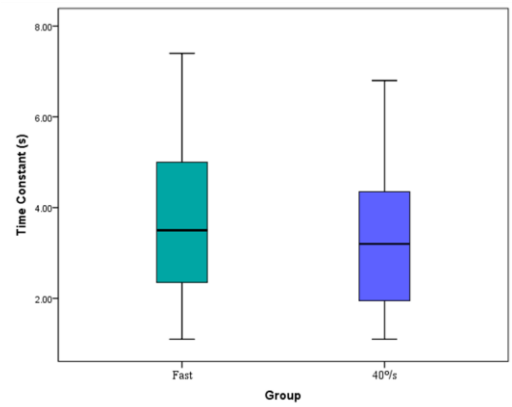


Table legend and tables

Table 1. Classification of central positional nystagmus

Classification	Features	Mechanism
Paroxysmal (<30s)	**Frequently multiplanar and aligned** • Downbeat nystagmus during SHH, lying down and Dix-Hallpike maneuver • Upbeat nystagmus when resuming upright position • Apogeotropic nystagmus after head-turning to either side while supine **Rarely observed** • Upbeat nystagmus during SHH, lying down and/or Dix-Hallpike maneuver • Upbeat nystagmus after head-turning to either side while supine • Geotropic nystagmus after head-turning to either side while supine	Disinhibition and enhanced responses of the secondary vestibular neurons during the positioning due to lesions involving the vestibulocerebellum
Persistent (>1min)	• Apogeotropic nystagmus after head-turning to either side while supine • Geotropic nystagmus after head-turning to either side while supine • Downbeat nystagmus during SHH, lying down, and/or Dix-Hallpike maneuver, and downbeat nystagmus usually increases in the prone position and decreases in the supine position • Upbeat nystagmus after head-turning to either side while supine	Erroneous neural processing within the velocity-storage circuit located in the brainstem and cerebellum that functions in estimating the angular head velocity, gravity direction, and inertial acceleration

SHH, straight head hanging

Table 2. Ocular motor findings in patients with paroxysmal downbeat central positional nystagmus

Pt	Etiology	Sex/Age	SN fix	SN non-fix	GEN	HSN	Saccade_H	Saccade_V
1	SCA 6	M/56	-	D	-	R+D	-	-
2	ACM	F/66	D	R+D	+(REB)	R→L+D	ND	ND
3	SCA	F/45	D	R+D	+(REB)	R+D	-	-
4	CA	F/70	-	L	+(REB)	-	Hypo(L)	Hypo(B)
5	CA	F/72	-	-	+(REB)	R→L	Hype(B)	Hypo(B)
6	SCA 1	M/62	-	D	-	R→L+D	-	-
7	EA2	F/22	D	R+D	-	L→R+D	ND	ND
8	CA	M/48	-	-	+	D	Hypo(B), slow	ND
9	CA	F/43	-	D	-	R+D	Hype(B)	Hypo(up),hype(down)
10	CA	M/72	-	L+D	-	L+D	Hypo(B)	ND
11	CA	M/47	-	U+OF	+	-	Hype(B)	Hypo(up),hype(down)
12	CVUE	M/67	D	D	+	D	-	-
13	EA2	M/16	D	D	+(REB)	L+D	-	-
14	EA	M/48	-	D	-	D	ND	ND
15	CA	F/55	-	-	+(REB)	-	Hypo(B)	ND
16	SCA	M/66	D	D	+	R→L+D	-	-
17	SCA	F/48	-	-	+(REB)	D	Hype(B)	ND
18	MSA-C	F/56	-	-	-	D	Hypo(B)	-
19	EA	M/63	-	-	+	R+D	-	Hypo(up),hype(down)
20	CVUE	M/55	D	D	+	R	Hype(B)	ND
21	SCA	M/65	D+SWJ	D+SO	+(REB)	L→R+D	Hype(B)	Hyper(B)

ACM, Arnold-Chiari malformation; APAN, aperiodic alternating nystagmus; B: both directions;CA, cerebellar ataxia; CVUE, central vertigo with unknown etiology; D, downbeat nystagmus; EA, episodic ataxia; F, female; GEN, gaze evoked nystagmus; HSN, head shaking nystagmus; Hype: hypermetria; Hypo: hypometria; L, left beating nystagmus; M, male; Max, maximum; MSA-C: multiple system atrophy-cerebellar subtype; MSO, macro saccadic oscillation; OF, ocular flutter; Pt, patient; R, right beating nystagmus; REB, rebound; SCA,

spinocerebellar ataxia; SN, spontaneous nystagmus; SN fix, spontaneous nystagmus with visual fixation; SN non-fix, spontaneous nystagmus without visual fixation; SO, saccadic oscillation; SWJ, square wave jerk; TC, time constant; +, present; -, normal or absent; →, change to

Table 3. Maximus slow pahse velocity (SPV) and time constant (TC) of downbeat nystagmus during slow and fast straight head hanging (SHH) tests

Pt	Manual				Rotatory chair							
	Max SPV		TC		Max SPV				TC			
	Slow	Fast	Slow	Fast	10°/s	20° /s	30° /s	40° /s	10°/s	20°/s	30°/s	40°/s
1	0.0	14.5	-	3.4	8.7	14.6	14.7	16.5	7.1	7.8	6.3	4.5
2	0.0	30.0	-	4.3	6.7	11.2	15.8	21.9	7.7	4.1	4.3	4.3
3	0.0	16.0	-	7.4	11.4	16.4	20.3	18.2	2.9	4.0	3.8	4.1
4	10.4	25.7	1.3	1.4	8.0	16.5	22.1	23.3	2.3	2.8	1.5	1.1
5	12.3	23.1	3.7	6.2	9.2	12.1	12.1	13.5	3.0	4.9	4.3	5.7
6	0.0	16.2	-	2.0	6.4	11.3	14.2	18.5	2.9	1.9	1.5	1.5
7	0.0	19.8	-	2.0	0.0	6.5	17.4	24.1	-	3.0	2.6	2.4
8	0.0	11.6	-	5.3	15.7	23.8	22.8	16.3	4.0	3.2	4.6	5.9
9	0.0	19.5	-	4.5	8.5	14.0	16.5	19.5	2.6	4.0	4.2	3.7
10	0.0	26.7	-	3.5	5.5	8.0	8.4	6.7	3.1	3.1	3.2	3.8
11	0.0	35.9	-	2.7	16.8	17.0	19.4	22.4	1.0	2.8	2.7	2.7
12	0.0	19.4	-	3.7	0.0	13.9	16.3	19.1	-	1.4	3.4	2.3
13	0.0	26.1	-	3.5	7.6	8.3	10.4	13.8	3.6	3.3	5.7	2.0
14	0.0	4.6	-	6.8	0.0	0.0	3.8	4.1	-	-	6.5	6.8
15	0.0	23.6	-	1.1	0.0	23.2	27.4	35.1	-	0.8	1.4	1.3

Table 3 Maximum slow pahse velocity (SPV) and time constant (TC) of downbeat nystagmus during slow and fast straight head hanging (SHH) tests (continued)

Pt	Manual				Rotatory chair							
	Max SPV		TC		Max SPV				TC			
	Slow	Fast	Slow	Fast	10° /s	20° /s	30° /s	40°/s	10°/s	20°/s	30°/s	40°/s
16	0.0	22.2	-	4.7	10.8	24.7	25.6	28.8	2.8	3.6	4.4	4.2
17	0.0	17.5	-	2.7	13.8	21.2	26.0	30.2	2.3	2.4	2.1	1.9
18	0.0	9.3	-	6.5	6.5	9.5	9.7	9.8	3.7	4.2	4.1	4.4
19	0.0	6.8	-	3.3	0	0	0	0	-	-	-	-
20	0.0	56.7	-	1.8	0	20.9	21.7	34.1	-	1.8	1.8	1.9
21	0.0	65.6	-	2.7	16.9	32.5	44.6	55.2	1.4	2.7	2.9	2.7

Pt, patient; SPV, slow phase velocity; TC, time constant; -, absent

국문 초록

배경: 중추체위안진(central positional nystagmus, CPN)은 양성돌발두위현훈(benign paroxysmal positional vertigo, BPPV)과 유사한 안진 양상을 보이기 때문에 임상의사의 관심이 많다. 중추체위안진은 병태생리학적으로 소뇌 또는 뇌간에 병변이 있는 경우 발생할 수 있다. 중추체위안진은 안진이 지속되는 시간에 따라 발작-중추체위안진(paroxysmal CPN)과 지속-중추체위안진(persistent CPN)으로 나눌 수 있다. 최근 연구에서 지속 및 발작 유형의 중추체위안진이 발생하는 기전에 대한 설명이 제시되었다. 지속-중추체위현훈은 머리의 회전, 중력 방향, 관성을측정하는 역할을 하는 뇌간과 소뇌에 위치한 속도저장회로(velocity-storage circuit)의 잘못된 신경처리로 설명할 수 있다. 반면, 발작-중추체위안진은 소뇌의 결절(nodulus)과 목젖(uvula)을 침범하는 병변으로 인해 체위를 변환하는 동안 이차 전정신경(secondary vestibular neurons)의 억제 및 강화 반응에 의해 생길 수 있다고 알려져 있으나, 발생 기전에 대해 앞으로 더 많은 연구가 필요하다.

목적: 머리를 똑바로 하고 뒤로 젖혀지게 눕는 자세인 straight head hanging (SHH)에 의해 유발되는 하방안진의 강도가 머리를 움직이는 속도에 의해 영향을 받는지 확인하여 발작-하방-중추체위안진의 발생 기전을 규명하고자 한다.

방법: 2018년 9월부터 2019년 7월까지 분당서울대학교병원 어지럼증센터에서 SHH 동안 발작-하방-중추체위안진이 유발되는 환자

21명을 전향적으로 모집하였다. 모든 환자는 수동자세변환 검사와 전동 회전의자를 이용한 자세변환 검사를 받았다. 수동자세변환검사는 빠른 속도와 느린 속도 두 가지 조건에서 시행되었으며, 회전의자를 이용한 자세변환검사에서는 10, 20, 30, 40 °/s의 서로 다른 회전 속도로 SHH 자세를 유도하였다. 자세변환검사로 유발된 안진은 비디오안구운동검사 장치를 이용하여 기록하였으며, 안진의 최대속도(maximum slow phase velocity)와 시간상수(time constant, TC)값을 결과 분석을 위한 변수로 사용하였다.

결과: 수동자세변환 검사로 유발된 발작-하방-중추체위안진은 빠른 속도에서는예외 없이 모든 환자에서 유발되었지만, 느린 속도의 자세변환 검사에서는 나타나지 않거나 안진의 강도가 약했다. 회전의자를 이용한 자세변환검사에서 회전 속도가 증가함에 따라 안진의 최대속도도 증가하였다. 회전속도 10°/s 에서 7.6°/s(0-16.9), 20°/s 에서 14.0°/s (0 - 32.5), 30°/s 에서 16.5°/s (0 - 44.6) 그리고 40°/s 에서 19.1°/s (0 - 55.2)였다 ($P < 0.001$, $P < 0.001$, $P = 0.004$; 선형 혼합 모델) 대조적으로, 발작-하방-중추체위안진의 시간상수 값은 회전속도에 따라 영향을 받지 않았다($P = 0.558$, $P = 0.881$, $P = 0.384$, 선형혼합모델).

결론: 머리 회전 속도와 안진 발생의 연관성은 발작-체위변환안진이 반고리관에 전달된 신호의 증강된 억제반동(exaggerated inhibitory rebound) 에 의해 발생할 수 있다는 가설을 뒷바침한다.

주요어 : 현훈, 안진, 중추체위안진, 하방안진, 기전

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